International Journal of Cardiology 133 (2009) 286–292

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Review

Protective roles of HDL, apoA-I and mimetic peptide on endothelial function: Through endothelial cells and endothelial progenitor cells

Qian Zhang[1], Ling Liu*,[1], Xiao-Yan Zheng

Department of Cardiology, the Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, PR China

Received 10 October 2008; accepted 8 November 2008
Available online 7 December 2008

Abstract

Endothelial dysfunction induced by various atherosclerotic risk factors can initiate the process of atherosclerosis. Endothelial progenitor cells (EPCs), which have been considered as the precursor of endothelial cells (ECs), play an important role in the maintenance of endothelial function. The inverse association between high-density lipoprotein (HDL) levels and the risk of coronary heart disease (CHD) events has been demonstrated. Furthermore, accumulating studies suggest an important role of HDL in preventing and restoring endothelial dysfunction. Also, the importance of apolipoprotein A-I (apoA-I) in protection against cardiovascular disease is widely researched. Recently, it is shown that HDL could protect cultured human EPCs in different ways. Here, we review the studies on the association between HDL, its functional components, including apoA-I and mimetic peptide, and endothelial function and the underlying mechanisms that have been carried out so far.

Keywords: High-density lipoprotein; Apolipoprotein A-I; Mimetic peptide; Endothelial function; Endothelial cells

1. Introduction

Endothelial cells (ECs), which form an endothelial monolayer between circulating blood and the rest of the vascular wall, play an important role in keeping normal endothelial function. Endothelial progenitor cells (EPCs), which have been considered as the precursor of ECs, can migrate and home to the site of injured ECs to divide into mature ECs and keep the integrity of the endothelial monolayer. Numerical and functional impairment of EPCs is also thought to contribute to endothelial dysfunction and the associated increase in cardiovascular risk. Furthermore, endothelial dysfunction has been proposed to be an early event of pathophysiologic importance in the atherosclerotic process.

Lots of clinical and epidemiological studies have demonstrated the inverse association between high-density lipoprotein (HDL) levels and the risk of coronary heart disease (CHD) events [1,2]. In prospective studies, the low serum levels of HDL cholesterol are independent risk factors of a second coronary event in patients with CHD [3,4]. The classic mechanisms of HDL protecting against the development of atherosclerotic cardiovascular disease include: (1) promotion of reversing cholesterol transport, (2) antioxidant property, (3) anti-inflammatory property.

Abbreviations: apoA-I, apolipoprotein A-I; APR, acute phase response; CHD, coronary heart disease; CNP, C-type natriuretics peptide; D-4F, 4F synthesized wholly from D-amino acids; ECs, endothelial cells; EDR, endothelium-dependent vasorelaxation; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; ET-1, endothelin-1; EPCs-CFU, EPCs-colony forming unit; HO-1, heme oxygenase-1; NO, nitric oxide; OxLDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PGI2, prostacyclin; SMCs, smooth muscle cells; SR-BI, scavenger receptor-BI; TF, tissue factor; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; vWF, Von Willebrand factor.

* Corresponding author. Tel./fax: +86 731 4895989.
E-mail address: feliuling@medmail.com.cn (L. Liu).
[1] Both authors contributed equally to the article.

0167-5273/$ - see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2008.11.034

In addition to above indicated mechanisms, the role of HDL in preventing and restoring endothelial dysfunction is also important in protecting against the development of CHD. It has been shown that infusion and overexpression of apolipoprotein A-I (apoA-I), the precursor and major protein moiety of HDL, significantly reduces atherosclerosis in animal models [5–9]. Recently, small, amphipathic helical apoA-I mimetic peptides composed of D-amino acids have been shown similar antiatherogenic properties. And the specific apoA-I mimetic peptide, 4F synthesized wholly from D-amino acids (D-4F), has been reported to improve HDL-mediated efflux and reverse cholesterol transport from macrophages, in conjunction with causing the formation of preβ HDL in apoE-null mice [10–11].

On the basis of recent findings, it is found that HDL has various direct effects on ECs [12]. However, relatively little is known about the effects of HDL on EPCs function. As EPCs dysfunction is known to be an early event in atherosclerosis and an important contributor to the pathogenesis of CHD [13,14], the present article focuses on the association between HDL, D-4F and ECs, and explains the role of HDL and apoA-I protects endothelial function through ECs and EPCs.

2. HDL, apoA-I and apoA-I mimetic peptide

HDL is the smallest and densest of the lipoproteins, it contains the A class of apolipoproteins (apoA), among which apolipoprotein A-I (apoA-I) is the most important. HDL cholesterol levels have an inverse correlation with incidence of ischemic heart disease as well as other atherosclerosis-related ischemic conditions. With the deep study about HDL, the important of functional components of HDL, such as apoA-I, is realized. It has been demonstrated that apoA-I can induce atherosclerosis regression in animal models [15,16].

ApoA-I has 243 amino acids. Since the initial report of success with apoA-$I_{Milano,}$ which is a variant of apoA-I identified in individuals who exhibit very low levels of HDL cholesterol [17,18], it has become clear that to produce a protein of this size, which can only be given intravenously, is difficult and expensive. Anantharamaiah et al. [19,20] discovered that the lipid-binding properties of this component of HDL were largely related to its class A amphipathic helices. After that, a systematic study was carried out to find the ideal peptide on the basis of physical–chemical properties and biological activity, as assessed in a tissue culture model of the human artery wall [21]. Later, the peptide with the most favorable physical–chemical characteristics and the highest biological activity contained four phenylalanine residues on the hydrophobic face and was designated 4F (F is the biochemical symbol for phenyl alanine) [21,22]. Use of 4F significantly improved the function of HDL in mice and monkeys [23]. When 4F was administered in combination with a statin, lesion size and macrophage content were reduced in mice with atherosclerosis, and lesions regressed in older mice [23].

2.1. Effects of apolipoprotein A-I mimetic peptide D-4F

a) Forms pre-β-HDL
b) Reduces lipid hydroperoxide concentrations in plasma, HDL, and LDL
c) Increases the activity of the antioxidant enzyme paraoxonase in HDL
d) Converts proinflammatory HDL to antiinflammatory HDL
e) Reduces LDL sensitivity to oxidation by artery wall cells in culture
f) Renders artery wall cells less capable of oxidizing LDL in culture
g) Reduces superoxide and increases nitric oxide accumulation production in cultured endothelial cells culture
h) Promotes cellular cholesterol efflux from cholesterol-loaded human macrophages
i) Reduces caspase-3, caspase-8 and caspase-9 activity and interleukin 6 levels in A549 cell cultured human type II pneumocytes after infection with influenza A virus stimulation
j) Reduces interleukin 6 levels in human type II pneumocytes in culture

3. Relationship between ECs, EPCs and endothelial dysfunction

The endothelium, formed by the monolayer of ECs, is not a passive blood-compatible lining for the containment of blood cells and plasma, but rather a metabolically active tissue that subserves a wide range of functions relating to vascular homeostasis. ECs, which line the vascular tree and adhere to a basement membrane, play an important role in the control of vasomotor tone, permeability, coagulation, growth of vascular smooth muscle cells (SMCs), and inflammatory responses by releasing or expressing various factors [24,25]. A balanced release of these bioactive factors facilitates vascular homeostasis. Endothelial dysfunction disrupts this balance, thereby predisposing the vessel wall to vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, pro-oxidation, thrombosis, impaired fibrinolytic function, vascular inflammation, and finally, atherosclerosis [26].

Maintenance of ECs layer of the vessel wall is essential for normal function of the vessel and prevention of vascular disorders, such as atherosclerosis [27]. Replacement of damaged ECs could occur through division of surrounding ECs. Furthermore, EPCs can differentiate into ECs if high cell turnover or increased oxidative stress takes place [28]. Therefore, EPCs might play an important role in maintenance of the endothelial layer in the vascular system.

In 1997, cells isolated from peripheral blood were found to display properties of ECs and progenitor cells, thus they were termed as EPCs [29]. EPCs are a circulating, bone marrow-derived cell population that express surface CD34, CD133, and vascular endothelial growth factor receptor 2 [28,29]. EPCs can be mobilized in response to vascular trauma or tissue ischemia,