OFFICIAL JOURNAL OF THE EUROPEAN
ATHEROSCLEROSIS SOCIETY
AFFILIATED WITH THE INTERNATIONAL
ATHEROSCLEROSIS SOCIETY
AND
THE SOCIETY OF Atherosclerosis IMAGING AND PREVENTION

ABSTRACTS
XIV International Symposium on Atherosclerosis
Rome, Italy, June 18-22, 2006
Tu-W16.1 HDL FUNCTIONS


Objective: In vitro studies have established that high density lipoproteins (HDL) from human plasma, as well as discoidal reconstituted HDL (rHDL) that contain apolipoprotein (apo) A-I, inhibit the cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin in cultured human umbilical vein endothelial cells [1]. More recently, we have shown that three serial infusions of discoidal rHDL, or lipid-free apoA-I administered prior to, at the time of and following an inflammatory stimulus inhibit acute inflammation in vivo [2]. The objectives of the present in vivo studies are to determine (i) if a single, low dose infusion of lipid-free apoA-I or discoidal rHDL, inhibits inflammation when administered prior to or at the time of the inflammatory stimulus, (ii) if a single dose of lipid-free apoA-I inhibits inflammation when administered after the inflammatory stimulus and (iii) if non-enzymatic glycation of apoA-I, as occurs in diabetic subjects, affects the anti-inflammatory properties of HDL.

Methods: Lipid-free apoA-I was isolated from human plasma by standard techniques. Discoidal rHDL containing phosphatidylcholine and apoA-I were prepared by the cholate dialysis method. Lipid-free apoA-I and the apoA-I in the discoidal rHDL were non-enzymatically glycosylated by incubation with methylglyoxal. Non-occlusive, silastic collars were inserted around the carotid arteries of normocholesterolemic New Zealand White rabbits. The animals received a single infusion of either saline, lipid-free apoA-I, or discoidal rHDL either 24 h prior to, at the time of, or at 3 or 9 h after collar insertion. Other animals received glycosylated lipid-free apoA-I or discoidal rHDL that contained glycosylated apoA-I 24 h prior to collar insertion. The animals were sacrificed 24 h after collar insertion and the carotid arteries were removed for analysis. Neutrophil recruitment into the intima-media and endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) were quantitated by immunohistochemistry.

Results: Insertion of a perivascular collar induced substantial endothelial expression of VCAM-1 and ICAM-1, as well as extensive infiltration of neutrophils into the artery wall of the saline-infused animals. When the animals received a single infusion of either lipid-free apoA-I or discoidal rHDL, at a dose of 8 mg apoA-I/kg either 24 h prior to or at the time of collar insertion, infiltration of neutrophils into the artery wall and endothelial expression of VCAM-1 and ICAM-1 decreased to baseline levels. Neutrophil infiltration into the artery wall and endothelial expression of VCAM-1, but not ICAM-1 was still inhibited effectively when the animals were infused with lipid-free apoA-I at doses as low as 2 mg/kg. Comparable results were obtained when lipid-free apoA-I was infused into the animals 3 h after collar insertion. Infiltration of lipid-free apoA-I 4 h after collar insertion inhibited infiltration of neutrophils into the artery wall and endothelial expression of VCAM-1, but not ICAM-1. When the animals were infused with non-enzymatically glycosylated lipid-free apoA-I, or with discoidal rHDL in which the apoA-I was non-enzymatically glycosylated, the inhibition of neutrophil infiltration into the artery wall and endothelial expression were both markedly attenuated.

Conclusions: A single infusion of lipid-free or lipid-associated apoA-I inhibits acute inflammation in rabbit carotid arteries, even when administered after an inflammatory stimulus. Glycosylated apoA-I, in either the lipid-free form, or as a constituent of discoidal rHDL, inhibits inflammation much less effectively than unmodified apoA-I.

References:

Funding: The National Health and Medical Research Council of Australia.

Tu-W16.2 CHOLESTEROL ESTER TRANSFER PROTEIN (CETP) PRODUCTION BY MACROPHAGES PROMOTES ATHEROSCLEROTIC LESION DEVELOPMENT

M. Van Hek1, D. Ye2, R.B. Hildebrandt3, J.K. Jrut4, M. Jutmanen5, T.J.C. Van Berkel1,2,3,4,5,6

Objective: Inhibition of CETP is considered a promising new therapeutic strategy to increase HDL, cholesterol levels and reduce atherosclerosis. Recent advances in CETP-specific inhibitors and the results of several CETP antagonists have led to the development of new CETP inhibitors. However, the potential of CETP inhibitors to reduce atherosclerosis in humans is still unknown.

Methods: In order to investigate the function of macrophage CETP in atherosclerotic lesions, LDL receptor knockout mice, which naturally lack CETP, were transplanted with bone marrow from CETP transgenic mice, which express the human CETP transgene under control of its natural promoter and major regulatory elements. Atherosclerotic lesion formation was induced by feeding a Western-type diet containing 0.25% cholesterol and 15% fat for 9 weeks.

Results: Macrophage CETP production increased a 1.8-fold (p<0.01) increase in atherosclerotic lesion development (56±12 to 4.25±0.95 mm²/mouse with macrophage CETP expression (n=9), as compared to 30±1.6 to 17±1.6 mm²/mouse in control mice (n=9)). The increase in lesion size was accompanied by an increase in VLDL/LDL cholesterol from 99±3.177 mg/dL to 176±1.67 mg/dL (p<0.01). Conversely, HDL cholesterol was decreased from 76±2.7 mg/dL to 53±7 mg/dL (p<0.05). Furthermore, the relative amount of the cholesterol-poor prebeta-HDL subspecies was 3-fold (p<0.0001) increased. The cholesterol redistribution was a direct effect of the substantial serum CETP activity levels (18±4 nmo/30 Min/mg) induced by macrophage CETP production.

Conclusions: Macrophage CETP is an important contributor to plasma CETP activity and promotes the development of atherosclerotic lesions.

Funding: This study was supported by the Netherlands Heart Foundation (2001T04).

Tu-W16.3 NORMAL ENDOTHELIAL FUNCTION IN CARRIERS OF THE APOLIPOPROTEIN A-I/MILANO MUTANT DESPITE LOW HDL-CHOLESTEROL LEVELS

M. Comnacchi, D. Baldassarre, M. Amato, S. Eiligni, C.R. Sistori, G. Francosca, L. Calabresi, C. Erre, G. Festi, Department of Pharmacological Sciences, University of Milano, Milano, Italy

Objective: Carriers of apolipoprotein A-I/Milano (A-I/M), the R173C mutant of apoA-I, are protected against cardiovascular diseases despite very low HDL-cholesterol (HDL-C) levels and hyperlipidemia. The aim of the present study was to investigate the endothelial function of A-I/M carriers, since low HDL-C levels have been associated with features of endothelial dysfunction.

Methods and Results: Plasma concentrations of soluble cell adhesion molecules (sCAMs), and forearm arterial compliance during reactive hyperemia were evaluated in 21 A-I/M carriers. 21 healthy subjects with low HDL-C, and 42 controls. Low HDL-C subjects had significantly higher plasma sCAM levels than controls. On the contrary, no differences were detected between A-I/M carriers and controls, indicating that HDL from A-I/M carriers may be more efficient than control HDL in inhibiting endothelial CAM expression. Thus, HDL were isolated from 6 A-I/M carriers and 6 controls, and their ability to inhibit VCAM-1 expression was tested in endothelial cells. HDL from A-I/M carriers were twice effective than control HDL in reducing TNF-Alpha-induced VCAM-1 expression, and the inhibition occurred at a transcellular level, as demonstrated by RT-PCR. Interestingly, no differences in arterial compliance during reactive hyperemia were detected between A-I/M carriers and controls.

Conclusion: Despite very low HDL-C levels, A-I/M carriers do not display features of endothelial dysfunction, such as the increase of circulating sCAM levels and the impairment of arterial compliance, probably because of a superior ability of A-I/M containing HDL to protect the endothelium.