EFFECT OF HIGH DENSITY LIPOPROTEINS ON THE EXPRESSION OF ADHESION MOLECULES ON ENDOTHELIAL CELLS

A Thesis submitted by

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ABSTRACT

High density lipoproteins (HDLs) protect against the development of coronary heart disease. There are several potential mechanisms which may account for the cardioprotective function of HDLs. These include their proposed role in the reverse cholesterol transport pathway, the capacity of HDLs to reduce the atherogenicity of low density lipoproteins by inhibiting their oxidative modification and, based on recent observations, they may be anti-atherogenic by virtue of their ability to inhibit the expression of adhesion molecules on endothelial cells. The investigations in this thesis centre on the effects of HDLs on the expression of endothelial cellular adhesion molecules with emphasis on the effects of HDL subpopulations, HDL composition, acute-phase HDLs and the effects of altering plasma HDLs on adhesion molecule expression in endothelial cells.

Chapter 3, shows that the HDLs from different subjects vary in their ability to inhibit vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells. This difference is attributable to differing proportions of HDL_2 and HDL_3. The HDL_3 subfraction is shown to be superior to HDL_2 as an inhibitor of the cytokine-induced expression of VCAM-1 in human umbilical vein endothelial cells (HUVECs).

The experiments in chapter 4 further investigate the HDLs mediated inhibition of VCAM-1 expression in endothelial cells by addressing the influence of apolipoprotein (apo) composition. Experiments show that altering the apolipoprotein composition on HDL_3 by replacing the apoA-I with apoA-II did not affect its ability to inhibit VCAM-1 expression. Experiments designed to show if the differences in

the inhibition of VCAM-1 expression by HDL_2 and HDL_3 may be due to differences in their protein or lipid components are presented. Neither the isolated HDL proteins nor the HDL lipids inhibit VCAM-1 expression when added separately to the endothelial cells. This is consistent with the results from other studies presented in chapter 4 in which lipid-free apoA-I and di-myristoyl-phosphatidylcholine (DMPC) vesicles alone have no inhibitory effect on VCAM-1 expression. However, when lipid-free apoA-I and DMPC are combined to make discoidal reconstituted HDLs (rHDLs), these particles are able to inhibit the cytokine-induced VCAM-1 expression on HUVECs .

The acute-phase protein serum amyloid-A (SAA) is predominantly carried on HDLs in the plasma and SAA has been shown to have potential proatherogenic properties. We originally hypothesised that HDLs that were associated with SAA would be less effective inhibitors of VCAM-1 expression in endothelial cells than unmodified HDLs. Experiments presented in chapter 5 show that this is not the case, with HDL_3 that is associated with SAA (SAA-HDL_3) being just as effective as unmodified HDL_3 in the inhibition of cytokine-induced VCAM-1 expression in HUVECs. Lipid-free SAA was also incubated with HUVECs and as is the case with lipid-free apoA-I, there is no inhibitory effect on cytokine-induced VCAM-1 expression.

Chapter 6 describes a preliminary study designed to determine whether raising the plasma HDL-C with the drug fenofibrate has any effect on the levels of serum soluble adhesion molecules in 20 subjects with type II diabetes mellitus. After 6 weeks of therapy with fenofibrate there is a significant reduction in soluble E-selectin

but no significant effect on soluble intracellular adhesion molecule-1 and soluble VCAM-1. These results are of sufficient interest to warrant a larger, randomised, double-blind, placebo controlled trial which is currently underway in our department.

This thesis expands upon the original discovery that HDLs inhibit the cytokine-induced expression of endothelial cell adhesion molecules and extends our understanding of this potential antiatherogenic function of HDLs.