THE ROLE OF ANTI-INFLAMMATORY PROPERTIES OF HIGH DENSITY LIPOPROTEINS IN ATHEROPROTECTION.

A thesis submitted by

STEPHEN JAMES NICHOLLS M.B.B.S. (ADEL.) FRACP

To the University of Adelaide

South Australia, Australia

For the degree of

DOCTOR OF PHILOSOPHY

Lipid Research Group

Heart Research Institute

and

Department of Medicine

University of Adelaide

SEPTEMBER 2004

TABLE OF CONTENTS

ABSTRACT

It is well established that high density lipoproteins (HDL) protect against the development of atherosclerotic cardiovascular disease. However, the mechanisms that confer this benefit remain unclear. In addition, to its well recognised ability to promote reverse cholesterol transport, in vitro studies and hypercholesterolaemic animal models have demonstrated that HDL possess anti-inflammatory, antioxidant and antithrombotic properties. Furthermore, in vitro studies have found that the anti-inflammatory properties of HDL are influenced by the phospholipid composition, suggesting a possible link to dietary fatty acid intake. The studies that contribute to this thesis explore the anti-inflammatory properties of HDL during an acute model of vascular injury in normocholesterolaemic rabbits, their ability to stabilise atherosclerotic plaque and their activity during the postprandial state.

The vascular protective properties of reconstituted HDL (rHDL) were investigated in a normocholesterolaemic rabbit model of acute vascular inflammation, the periarterial collar. Infusions of rHDL profoundly inhibited the recruitment of neutrophils into the arterial wall in response and generation of reactive oxygen species in response to application of the periarterial collar. In addition, the early expression of proinflammatory adhesion molecules and chemokines by the endothelium was inhibited. These profound effects of discoidal HDL were seen in the absence of elevating plasma HDL and appeared to be independent of their ability to promote cholesterol efflux.

It is recognised that one origin of discoidal HDL is from the metabolism of chylomicrons. The effect of infusing phospholipid specific chylomicron-like emulsions on the anti-inflammatory properties of HDL was investigated. Following infusion of these emulsions, isolated HDL demonstrated a greater ability to inhibit the in vitro expression of the adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1), by endothelial cells in response to cytokine stimulation. This suggests that the functional properties of HDL may change during the postprandial state.

These properties of HDL were then investigated in a hypercholesterolaemic, aortic balloon denudation rabbit model of established atherosclerosis. Infusions of HDL were comparable to atorvastatin in their ability to rapidly promote the formation of a more stable plaque phenotype, characterised by an increase in smooth muscle cells, reduction in matrix metalloproteinases and increase in the anticoagulant thrombomodulin. The effect of altering the composition of rHDL on these properties was then investigated. The ability of rHDL to promote plaque stabilisation was diminished when rHDL contained the protein apolipoprotein A-II.

The effect of the postprandial state on the anti-inflammatory properties of HDL was investigated in humans. Following the consumption of a fat enriched meal, the ability of isolated HDL to inhibit in vitro expression of VCAM-1 by activated endothelial cells was studied. When the meal comprised a polyunsaturated fat, the anti-inflammatory property of HDL improved. In contrast, when a saturated fat was consumed, the anti-inflammatory property of HDL diminished. These results suggest that dietary fatty acid composition can have a profound impact on atheroproperties of HDL.

This thesis expands our knowledge of the contribution of the in vivo anti-inflammatory properties of HDL. The results suggest that small amounts of HDL can have a profound beneficial influence in the setting of acute vascular inflammation and established atherosclerotic plaque. This highlights the important role that HDL plays in both the early and advanced stages of atherogenesis. In addition, the consumption of dietary fat has a striking impact on this activity, providing another mechanism by which the consumption of dietary fat modifies the risk of atherosclerotic cardiovascular disease.