Plasma Lipoproteins and Coronary Heart Disease

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ABSTRACT

Both plasma low-density (LDL) and high-density lipoproteins (HDL) have been associated with the genesis of cardiovascular disease. Recent studies with cells grown in culture have suggested a regulatory role of these lipoproteins in cellular cholesterol metabolism and pointed at abnormalities resulting from deviations of these regulatory processes. The precise relationship between these observations in vitro and the atherogenic process remains open to investigation.

Introduction

This brief account deals with an examination of current concepts of the relationship between plasma lipoproteins and atherosclerosis, with particular reference to coronary heart disease (CHD). Circulating lipoproteins have long been implicated in the pathogenesis of the atherosclerotic process; the underlying mechanisms, however, remain unknown. The low-density lipoproteins (LDL) have usually been regarded as the major culprits in this process. Recent studies have brought into focus the possible pathogenetic role of another group of plasma lipoproteins, those which comprise the high-density lipoproteins (HDL). Both the LDL and HDL theories will be analyzed, and attempts will be made to reconcile or integrate the two concepts.

LDL Theory

Since the pioneering ultracentrifugalf studies by Gofman et al., the elevation of plasma low-density lipoproteins (LDL) has been associated with the pathogenesis of atherosclerosis and coronary heart disease (CHD) in particular. The relationship between hyperlipoproteinemias involving either very low density lipoproteins (VLDL) or LDL, or both, was also stressed by the clinical studies of Fredrickson et al. based on their proposed phenotyping system. In

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later studies, Goldstein et al,\textsuperscript{16,17} through an analysis of a large group of survivors of myocardial infarction, obtained evidence of a genetic relationship between hyperlipidemias and CHD. Slack\textsuperscript{31} also showed that patients with familial hyperlipoproteinemia have an increased risk of ischemic heart disease. Thus, from these and many other studies,\textsuperscript{34} it appears that inherited hyperlipoproteinemic states expressed by either hypercholesterolemia or hypertriglyceridemia are important predisposing, although not necessarily determining, factors in CHD. In terms of acquired factors, the dietary theory has also stressed the role of the increase in circulating cholesterol and LDL levels in atherosclerosis; this concept has led to the adoption of diets low in saturated fats and cholesterol and enriched in polyunsaturated fatty acids.\textsuperscript{1,23}

Since the increase of plasma cholesterol levels is thought to increase the incidence of CHD,\textsuperscript{12} and since LDL are the major carriers of circulating cholesterol, the measured concentration of these lipoproteins has been utilized as a diagnostic or predictive index of atherosclerosis. The earliest work in this direction was that by Gofman et al\textsuperscript{14} who, in a study of 104 patients, associated the elevation of the plasma S\textsubscript{10-20} LDL class to myocardial infarction. These early studies, carried out in the analytical ultracentrifuge, were later followed by other methods of lipoprotein measurements which included chromatographic and electrophoretic techniques, polyanion precipitation, as well as turbidimetric techniques.

More recently, very sensitive and specific immunological techniques, particularly radio- and electroimmunoassay techniques,\textsuperscript{22} have been developed for the measurement of apolipoprotein B, the major protein of LDL. The introduction of these techniques for the study of the various apolipoproteins has opened a new era of investigation which is going to include, besides apolipoprotein B, other apoproteins found to be present in certain hyperlipoproteinemias.\textsuperscript{19} If the postulate is accepted that high levels of circulating LDL are related to atherosclerosis, then the cause-effect relationship must be explained. An increased filtration of LDL from plasma into the aortic tissue could be taken as a plausible mechanism; but recent studies on the response of cultured cells to lipoproteins make this hypothesis appear too simplistic.

According to Goldstein and Brown,\textsuperscript{15} peripheral cells such as blood lymphocytes, cultured skin fibroblasts or aortic smooth-muscle cells possess an elaborate biochemical pathway, the LDL pathway, that regulates uptake, storage and synthesis of cholesterol. The first step in this process would be the binding of LDL to specific cell surface receptors, followed by the uptake of these lipoproteins by endocytosis and their degradation by lysosomal hydrolases. These processes would lead to the release of LDL cholesterol which, by an unspecified mechanism, suppresses endogeneous cholesterol production by the cell.

According to this theory, non-hepatic cells are capable of controlling the number of cell-surface LDL receptors, which represent a fine mechanism for control of cholesterol entry and accumulation within the cell. Thus, by regulating the number of cell-surface receptors, the cells would assure, at the same time, an adequate supply of this sterol and a protective mechanism against overaccumulation.\textsuperscript{18} Under physiological conditions, the mean level of LDL in plasma in the interstitial fluid would be maintained within the normal range by appropriate regulation of the number of cell-surface receptors. If the level of circulating LDL is abnormally high, however, the LDL pathway of peripheral cells such as aortic smooth muscle cells will be saturated, leading to an uptake by an alternative route, namely, a phagocytic, receptor-
independent process, and to an uncontrolled accumulation of cholesteryl esters. According to this hypothesis, atherosclerosis would occur whenever the LDL-receptor mechanism fails to regulate the LDL and thus entry into the cell. Some circumstantial evidence appears to support this challenging concept, but stronger support is needed, particularly from *in vivo* studies.

**HDL Theory**

In 1975, Miller and Miller postulated a correlation between levels of circulating HDL and atherosclerotic disease.26 This hypothesis has since received support from the epidemiological studies of Castelli et al,7 Berg et al,4 Gordon18 and also from the observation that subjects with an increased risk of CHD, i.e., those with hyperlipidemia, obesity and diabetes mellitus, exhibit low levels of circulating HDL.26 Moreover, Hsa et al20 have reported that the uptake of solubilized, crystalline cholesterol by human serum is significantly decreased in atherosclerotic disease and that an important part of the "reserve cholesterol binding capacity" resides in the HDL fractions.

In middle-aged and elderly persons, the incidence of CHD was found to be inversely proportional to the plasma levels of circulating HDL.7,30 In turn, patients with hypercholesterolemia, obesity or diabetes mellitus, all having low HDL levels, were found to have an increased risk of CHD.26 Patients with clinical CHD have also been reported to exhibit low levels of apolipoprotein A-I, the major apoprotein of HDL.4 Thus, it appears that HDL might have a protective effect against atherosclerosis. Further support for this conclusion derives from the following observations: (A) Studies carried out on 6,596 men in the city of Tromso, Norway have indicated that low plasma LDL levels are a common antecedent of clinical CHD.29 (B) Premenopausal women, who have a relatively higher level of plasma HDL than men, are relatively free of atherosclerosis.29 (C) Patients with hyper-alphalipoproteinemia have an above-average life expectancy.13 (D) Children of CHD patients have plasma cholesterol levels lower than those in children of healthy parents.9 (E) Physical activity, which has been shown to increase plasma HDL,2,6,8,25 has a beneficial effect on the incidence of CHD.

The anti-atherogenicity of HDL, suggested by the clinical studies outlined, could be explained by the proposal that plasma HDL delivers for catabolism to the liver, via the lecithin-cholesterol acyl transferase mechanism, all of the cholesterol derived from tissues, including the arterial wall.12 It has also been suggested that HDL, by competing with the LDL receptor mechanism, may slow the atherogenic process5 and may favor the egress of cholesterol from cultured skin fibroblasts or aortic smooth-muscle cells.33 These experimental results, although not yet conclusive, would appear to provide a plausible rationale for the beneficial effects of HDL on the atherosclerotic process.

**Can the LDL and HDL Theories Be Reconciled?**

Evidence obtained from studies *in vivo* indicates that removal of LDL from plasma occurs mainly in extrahepatic tissues.32 Based upon work on cultured cells, the mechanism has been attributed to the LDL pathway which recognizes steps of binding, internalization and degradation. Alteration of this process would lead to elevation of plasma LDL and to hypercholesterolemia. The pool of exchangeable cholesterol in man has been reported to be inversely related to the plasma HDL cholesterol concentration,27 and evidence is now available from studies in cultured and normal human fibroblasts that the processes of binding, internalization and degradation also apply to HDL, but at
sites different from those of LDL.\textsuperscript{24,28} This conclusion is based on the finding that only a very small amount of HDL is bound to the high-affinity LDL receptor.

According to Miller et al.,\textsuperscript{27} LDL can increase the cholesterol content in cells and also selectively inhibit sterol biosynthesis, but HDL has neither of these effects. On the other hand, the promotion of efflux of cholesterol from cells by HDL,\textsuperscript{3,33} is a process which, according to Fogelman et al.,\textsuperscript{10} might regulate intracellular cholesterol synthesis, at least in granulocytes. All of these observations \textit{in vitro} indicate that intracellular cholesterol can be regulated by both LDL and HDL, although by independent, specific high-affinity membrane sites or receptors. It is likely that, as studies progress, a relationship between these two processes will be discovered, and that this will be found to form the basis of a fine regulation of cellular cholesterol synthesis and efflux \textit{in vitro}. Whether or not these phenomena observed \textit{in vitro} participate in the homeostasis of the plasma cholesterol levels \textit{in vivo} remains open to investigation.

It is important to have an understanding of hepatic and extra-hepatic cholesterol metabolism and regulation as well as of the factors controlling cholesterol efflux and uptake by the cells. Thus far, the receptor-mediated LDL pathway postulated by Goldstein and Brown\textsuperscript{15} appears to provide an adequate explanation for the elevation of LDL observed in patients with homozygous or heterozygous familial hypercholesterolemia. Whether or not dyslipoproteinemias, particularly those of the familial type, can be ascribed to an alteration in function of specific membrane receptors remains to be established.

References


