

Plasma Lipoproteins and Atherosclerosis: Accomplishments and Opportunities

Advances in Vascular Biology—Volume 5: Plasma Lipids and Their Role in Disease

Edited by Philip J. Barter and Kerry-Anne Rye

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In one sense, the topic of plasma lipids and their role in disease is a mature field of biomedical investigation, with successful clinical applications to diagnosis, prevention, and treatment. At the same time, the field is still advancing rapidly, particularly with the use of transgenic models of disease that are illuminating important fundamental and clinical issues and the consistent evidence that plasma lipid-lowering has salutary effects in a variety of clinical settings. As indicated in the editors' preface to this text, abnormalities of plasma lipid transport "reflect an interaction between genes and a variety of lifestyle factors," several of which "lead to severe clinical disease." Thus, they direct this multiauthored text to interested physicians as well as scientists.

Plasma lipids are carried mainly in macromolecular complexes known as lipoproteins, in which nonpolar lipids are shielded from the aqueous environment by polar lipids and specific proteins (apolipoproteins). A notable exception is the albumin-fatty acid complex. Nonesterified (free) fatty acids bound to albumin represent large amounts of energy-rich, readily oxidizable lipid carried through the plasma, mainly from adipose cells to muscle and liver. Although this book is concerned with plasma lipids and disease, little attention is paid to altered rates of free fatty acid transport that are central to several secondary dyslipoproteinemias, such as in diabetes mellitus. Abnormalities of free fatty acid transport also contribute to lipoprotein abnormalities associated with obesity and perhaps with certain primary disorders of plasma lipoproteins, such as familial combined hyperlipidemia. The related and controversial issue of acylation-stimulating protein (complement factor 3 desarg), genetic abnormalities of which have been proposed to cause hyperapobetalipoproteinemia by increasing the flux of free fatty acids into the liver (Kildsgaard et al., 1999), is ignored.

Even more surprising in a book directed in part to physicians is the paucity of material on nutritional influences on plasma lipids and disease. Atherosclerotic disease, the major cause of death in Western countries, is directly related to plasma cholesterol concentration. Among the world's populations, plasma cholesterol varies widely and is influenced primarily by diet. Indeed, it is generally held that differences in dietary patterns are the primary cause of the observed several-fold differences in coronary heart disease mortality among the world's populations. The major dietary components responsible for these differences are the long-chain fatty

acids present in dietary fat (triacylglycerols). Animal fats rich in saturated long-chain fatty acids and cholesterol raise the concentration of lipoproteins containing apolipoprotein B-100 by downregulating low-density lipoprotein (LDL) receptors in hepatic parenchymal cells. These lipoproteins are not only synthesized but also largely undergo terminal catabolism in these cells. Controversy is continuing as to whether the amount of total dietary fatty acids or only that of saturated fatty acids should be reduced. Also, plasma lipids are affected differently by n-6 as opposed to n-3 polyunsaturated fatty acids. Studies analyzing electrophysiologic effects on myocytes indicate that dietary intake of n-3 fatty acids may prevent fatal cardiac arrhythmias induced by ischemia (Kang and Leaf, 2000). These and related topics central to prevention and treatment of atherosclerotic disease receive little or no consideration.

The dramatically reduced incidence of heart attacks and strokes due to plasma lipid-lowering drugs in healthy persons as well as those affected by atherosclerotic complications is addressed only briefly in several chapters. The relationship between lipid-lowering and the clinical benefits of treatment with β -hydroxy β -methyl coenzyme A reductase inhibitors known as "statins" is somewhat controversial. Direct effects of these drugs on vascular function have been proposed to account for the impressive clinical benefits of statin therapy that seem to outweigh effects upon lipid-lowering. Even greater benefit may, however, accrue from a procedure known as "LDL apheresis," whereby lipoproteins containing apolipoprotein B are selectively removed by absorption onto affinity reagents (Kajinami and Mabuchi, 1999). Also, the mechanism of action of drugs of the "fibrate" class is currently receiving much attention. Fibrates are used to reduce the concentration of plasma triacylglycerols, by increasing efficiency of the catabolism of triacylglycerol-rich very low-density lipoproteins (VLDL); these compounds cause hypertrophy and hyperplasia of peroxisomes in rodent liver. Recent studies have shown that they act by stimulating the production of peroxisome proliferator activator receptors (PPARs), thereby reducing the synthesis of certain apolipoproteins in liver and increasing that of lipoprotein lipase in adipose tissue (Schoonmans et al., 1997). PPARs and their regulation, which have broad implications for the regulation of lipoprotein-lipid metabolism, are hardly mentioned.

This volume begins with two introductory overview chapters on normal plasma lipoprotein transport and metabolism and dyslipidemias, followed by a review of population and family evidence relating plasma lipids and lipoprotein concentrations to atherosclerotic disease. Most of the other chapters deal with atherogenic and antiatherogenic lipoproteins and their receptors, and with lipases and lipid-transfer proteins. There are also chapters on apolipoprotein E (treating not only plasma lipoproteins but also the role of the role of apolipoprotein E produced in the central nervous system in Alzheimer's disease), on lipid/lipoprotein oxidation, and on endothelial function in dyslipoproteinemias.

Two chapters on atherogenic lipoproteins address the extensively investigated subject of chylomicron remnants and LDL. The latter is concise, but reasonably comprehensive in considering important differences

among species of LDL differing in size and density, potentially atherogenic modifications including lipid-oxidation, and the role of LDL in formation of arterial fatty streaks and complicated plaques. The former presents an enthusiast's view of the importance of chylomicron remnants in atherogenesis, focusing primarily on the author's work. The chapter contains numerous controversial statements such as the suggestion that as much as 15 g of cholesterol may be transported in plasma chylomicrons daily, and that chylomicron remnants are a "primary" atherogenic lipoprotein. The author of this chapter correctly points out that humans are in a postprandial (variably chylomicronemic) state most of the time, but fails to note that postprandial changes in liver-derived VLDL are more pronounced. Although there is considerable evidence for the atherogenicity of certain subfractions of VLDL, neither in this chapter nor elsewhere in this volume is this topic discussed.

Two chapters on high-density lipoproteins (HDL) and their receptors provide useful summaries of these important topics. That the antiatherogenic property of HDL cannot clearly be ascribed to promotion of "reverse cholesterol transport" (from extrahepatic cells to liver) or to other biologic activities is clearly described. Failure to address the association of scavenger receptor B-1 with caveolae and the emerging data on the regulation of caveolin by cholesterol (Fielding and Fielding, 1997), clearly relevant to reverse cholesterol transport, is a shortcoming in a chapter written in 1998. In 1999, mutation of the ATP binding cassette transporter 1 was shown to be the genetic defect in Tangier disease, which leads to storage of cholesteryl esters in reticuloendothelial cells and extremely low levels of circulating HDL (Hobbs and Rader, 1999).

Three well-written chapters address lipid-transfer proteins: microsomal triglyceride transfer protein, plasma cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP). The discussion of settings in which CETP may be pro- or antiatherogenic is particularly insightful. The role of PLTP, which has been difficult to assess, has become clearer from recent observations on PLTP knockout mice. These animals display greatly reduced HDL levels and other abnormalities consistent with impaired transfer of polar lipids from VLDL and chylomicrons to HDL (Jiang et al., 1999).

The chapter on endothelial lipases affecting plasma lipid transport provides a useful introduction to this topic. However, the emerging roles of hepatic lipase in remodeling of LDL and well as HDL species, relevant to atherosclerotic disease (Zambon et al., 1999) deserve more emphasis.

The authoritative chapter on apolipoprotein E is more comprehensive in considering several complex issues. Terminology in this field can be confusing, even to those working in it. In this chapter, terms such as sequestration, trapping, docking, and receptor binding are not always well defined. Here, heparan sulfate proteoglycans are elevated to the status of a receptor, although their role in clearance of remnant lipoproteins is stated to be one of sequestration. By contrast, hepatic lipase, which may also sequester chylomicron remnants is here relegated to a secondary, processing role. Oxidation of plasma lipids and apolipoproteins is the subject of a scholarly treatise in which the authors' evidence that

α -tocopherol can promote rather than prevent lipid peroxidation under circumstances that may be biologically relevant is well documented.

The final chapter discusses effects of plasma lipoproteins on endothelial function, mainly related to the capacity to generate NO. This is a welcome addition to such a book, but one might have hoped for an additional chapter on lipoproteins and thrombosis, and more in-depth discussion of the role of lipoproteins in atherosclerotic plaque-rupture and stabilization. A compilation of reviews covering this rapidly moving field is useful, but the discerning reader will have to search elsewhere for up-to-date consideration of a number of important aspects of plasma lipids and disease.

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Understanding Sex in the Brain

Drive: Neurobiological and Molecular Mechanisms of Sexual Motivation

By Donald Pfaff

Cambridge, MA: MIT Press (1999). 316 pp. \$90.00

Sexual motivation has always been a hot topic of scientific and cultural interest. Thousands of years of human history have been spent trying to understand and manipulate it. We have lusted after it in the form of drugs, potions, glands, scents, clothing, fetish objects, music, lighting, and correct phrases. Earlier this century, pioneers like Steinach, Stone, Young, Boling, Blandau, and Beach found part of it in the secretions of gonadal tissues, the steroid hormones testosterone, estrogen, and progesterone. Later, Beach, Davidson, Larsson, and Södersten found that gonadal steroids not only maintain the function of peripheral tissues, but act on the brain to change the motivational state of the organism. By the late 1960s, research into the nature of steroid hormone action in the brain had blossomed into the discipline of neuroendocrinology; one of the founders of this discipline was Donald Pfaff.