Advances in Lipid Research

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PREFACE

This volume of *Advances in Lipid Research* is devoted to several special areas of lipid research which are becoming important; new frontiers of established areas of interest are also treated.

The first chapter discusses the application of electron microscopic techniques to the analysis of plasma lipoproteins, an entirely novel way of studying lipoprotein structure. The second article provides a new look at a topic that has piqued scientific interest for a long time—possible modification of reticuloendothelial function by lipids. Present awareness of the role played by lipids in membrane structure and function introduces new aspects to this field. The role of lipids in cellular, humoral, and immune responses is discussed in the second chapter. The third contribution summarizes current knowledge of the microsomal enzymes of sterol biosynthesis. With the extension of studies of lipid synthesis to tissue culture and with new methods of separation and identification of sterols, this paper should be useful to workers in a number of areas. The fifth chapter provides the latest information on one aspect (enzymatic synthesis and degradation) of glycerol lipids which contain ether bonds. This type of lipid has been found in an increasing number of tissues and cells, and its metabolic role is only now being delineated. Brain and nervous tissue research continues to expand with work covering normal development as well as genetic defects. Two chapters explore lipid neurochemistry in depth: the fourth chapter covers brain lipids (fatty acids, phospholipids, sphingolipids, galactosyl lipids, and sterols), whereas the sixth chapter is somewhat broader in scope and discusses lipids of the entire nervous system and their variation with age. Both articles contribute greatly to the knowledge of lipid neurochemistry.

Rodolfo Paoletti
David Kritchevsky

CONTENTS OF PREVIOUS VOLUMES

Volume 1

Volume 2

Volume 3

Volume 4

Volume 5

Volume 6

Volume 7

Volume 8

Volume 9

CONTENTS

Microsomal Enzymes of Sterol Biosynthesis

James L. Gaylor

Brain Lipids

Robert B. Ramsey and Harold J. Nicholas

Enzymatic Systems That Synthesize and Degrade Glycerolipids Possessing Ether Bonds

Fred Snyder

Lipids in the Nervous System of Different Species as a Function of Age: Brain, Spinal Cord, Peripheral Nerve, Purified Whole Cell Preparations, and Subcellular Particulates: Regulatory Mechanisms and Membrane Structure

George Rouser, Gene Kritchevsky, Akira Yamamoto, and Claude F. Baxter

Application of Electron Microscopy to the Study of Plasma Lipoprotein Structure[1]

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I. Introduction

A. Definition of Lipoproteins

Plasma lipoproteins are macromolecules composed of proteins and lipids. They perform the important function of transporting complex lipids (triglycerides, phospholipids, unesterified cholesterol, and cholesteryl esters) in the plasma. The transported lipids are biologically important in the energy metabolism of tissues and in the structure of cell membranes.

The physical, chemical, and immunological properties of the various lipoprotein classes and their proteins (apolipoproteins) have received much attention in the past few years and several reviews have recently been published (Fredrickson *et al.*, 1967; Schumaker and Adams, 1969;

[1] This work was supported by Research Grants HE 12710-02 and HE 10878-05 from the National Heart and Lung Institute, U. S. Public Health Service, Bethesda, Maryland, and by the U. S. Atomic Energy Commission.

Zilversmit, 1969; Margolis, 1969; Scanu, 1965, 1969; Nichols, 1969). At this time, however, there is no comprehensive survey of available data on the microscopical visualization of plasma lipoproteins. Investigation of the various classes of plasma lipoproteins with the electron microscope has proceeded rapidly in the past few years, and in the present review we will examine the contribution of diverse electron microscopical approaches to our understanding of their morphology.

B. Scope of This Review

The present review will focus on the morphological properties of lipoproteins as shown by various electron microscopic techniques including fixation and shadowing, fixation and sectioning, freeze-etching, and negative staining. The main emphasis will be on the isolated lipoprotein fractions since such fractions are physically and chemically well defined. The lipoprotein fractions discussed are mainly those from human plasma; however, where it pertains, the review will consider plasma lipoproteins from other mammalian species. Since lipoproteins isolated from plasma and serum appear to be identical in their chemical and physical properties, the terms "plasma" and "serum" will be used interchangeably.

The aim of this review is twofold: (1) to point out the capabilities as well as the limitations of the various electron microscopic techniques in the analysis of lipoprotein structure, and (2) to stimulate further studies on morphological aspects of lipid-protein interactions in plasma lipoproteins as well as in model systems containing specific lipids and proteins.

II. Physical and Chemical Characterization of Plasma Lipoproteins

Based on many studies, four major classes of human plasma lipoproteins have been characterized by preparative and analytical ultracentrifugation and by electrophoresis. These classes are chylomicrons, very low density lipoproteins (VLDL), low density liproproteins (LDL), and high density lipoproteins (HDL). Each of these classes can, furthermore, be ultracentrifugally fractionated into subclasses on the basis of their density. According to their electrophoretic migration on paper, the HDL are designated α-lipoproteins, LDL are designated β-lipoproteins, and VLDL are designated pre-β-lipoproteins. The chylomicrons do not migrate in the electrical field and remain at the origin.

The operational classification and compositional properties of the major classes of plasma lipoproteins are summarized in Table I.

Table I: Classification and Properties of the Major Classes of Plasma Lipoproteins

	Chylomicrons	Very low density lipoproteins (VLDL)	Low density lipoproteins (LDL)	High density lipoproteins (HDL)
Preparative ultracentrifugal density classification[a]	d < 0.95 gm/ml	d 0.95–1.006 gm/ml	d 1.006–1.063 gm/ml	d 1.063–1.21 gm/ml
Analytic ultracentrifugal flotation rate classification[b]	$S_f > 400$	S_f 20–400	S_f 0–20	$F_{1.20}$ 0–9
Paper electrophoretic migration classification	Chylomicrons	pre-β	β	α
Average composition[c]				
Phospholipid	7	19	22	24
Unesterified cholesterol	2	7	8	2
Cholesteryl esters	5	13	37	20
Triglyceride	84	51	11	4
Protein	2	8	21	50
Major protein (apolipoprotein) constituents[d]	Probably include: apoLP-ser apoLP-glu apoLP-ala$_1$ apoLP-ala$_2$	apoLDL apoLP-ser apoLP-glu apoLP-ala$_1$ apoLP-ala$_2$	apoLDL	apoLP-glnI[e] apoLP-glnII[f]

[a] d. values designate density ranges of the lipoprotein classes as isolated from plasma by sequential preparative ultracentrifugation.

[b] S_f values are ultracentrifugal flotation rates expressed as Svedbergs (10^{-13} cm/sec/dyne/gm) in a solution of density 1.063 gm/ml at 26°C (1.748 molal NaCl). $F_{1.20}$ values are flotation rates expressed in Svedbergs in a solution of density 1.20 gm/ml (Ewing *et al.*, 1965).

[c] Major compositional constituents are listed; where available, content of nonesterified fatty acids was included in compositional computation but not listed in table (Hatch and Lees, 1968; Oncley and Harvie, 1969).

[d] Protein constituents termed apolipoproteins (apoLP) are designated by their carboxyl terminal amino acids, abbreviated as follows: ala (alanine), gln (glutamine), glu (glutamic), ser (serine) (Fredrickson, 1969; Gotto *et al.*, 1971; Nichols *et al.*, 1972; Levy *et al.*, 1971; Eisenberg *et al.*, 1972).

[e] Corresponds to ApoA-I of Kostner and Alaupovic (1971); R-thr of Shore and Shore (1969); Fraction III of Scanu *et al.* (1969); and Band C of Rudman *et al.* (1970).

[f] Corresponds to ApoA-II of Kostner and Alaupovic (1971); R-gln of Shore and Shore (1969); Fraction IV of Scanu *et al.* (1969); and Band D of Rudman *et al.* (1970).