Hyperlipidemia
Diagnosis and Therapy

Edited by

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重庆医科大学附属第一医院图书馆藏专用章

Grune & Stratton
A Subsidiary of Harcourt Brace Jovanovich, Publishers

New York San Francisco London

Library of Congress Cataloging in Publication Data

Main entry under title:

Hyperlipidemia.

(Chemical cardiology monographs)
Includes bibliographical references and index.
1. Hyperlipoproteinemia. 2. Hyperlipemia.
I. Rifkind, Basil M. II. Levy, Robert I., 1937-
III. Series. [DNLM: 1. Hyperlipemia. WD200 H99
RC632.H88H96 616.3'9 77-4887
ISBN 0-8089-1006-X

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Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Distributed in the United Kingdom by
Academic Press, Inc. (London) Ltd.
24/28 Oval Road, London NW 1

Library of Congress Catalog Number 77-4887
International Standard Book Number 0-8089-1006-X

Printed in the United States of America

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Preface

Many significant advances have recently taken place in our understanding of the plasma lipids and disease. They range from exciting epidemiological observations showing an inverse relationship between high density lipoprotein levels and coronary heart disease to detailed biochemical findings which begin to indicate how lipoproteins interact and exert their physiological and pathophysiological effects. Nevertheless, much remains to be known, such as in the areas of prevention and treatment. These gaps in our knowledge are reflected in the occasional divergence of opinion between different authors in the present volume. Rather than encouraging a monolithic standardized approach, we have allowed for some overlap of topics and encouraged resulting dissonance to occur.

These advances have been accompanied by a considerable growth, both nationally and internationally, in the resources and knowledge available for the diagnosis and management of hyperlipidemic disorders. "Lipid clinics" now exist in most large communities either alone or in conjunction with clinics that handle other metabolic disorders such as diabetes mellitus. Hyperlipidemia is recognized with increased frequency as facilities and the awareness of its presence expand. Our objective in assembling this volume is to provide an authoritative and comprehensive account of the diagnosis and management of hyperlipidemic and hyperlipoproteinemic states. The many authors in the present text were selected on the basis of their intimate knowledge and experience of these disorders and of their mechanisms, treatment and control.

We have not restricted the topic to hyperlipidemia per se, a somewhat arbitrary concept in any case, but have considered lipids and lipoproteins in general, and their disease relevance. The public health consequences of plasma cholesterol are not confined to the relatively small number of subjects to be found at the upper tail of the distribution, but also involve, from a statistical standpoint, the rest of the lipid distribution. Prevention of coronary heart disease through lipid lowering must take into account the larger number of these so-called normolipidemic subjects as well as the smaller number of high risk hyperlipidemic individuals. These considerations have led us to expand the topics beyond the individual hyperlipoproteinemias. Current epidemiological research and a review and evaluation of clinical trials of lipid lowering have therefore been included.

Such an approach illustrates the multidisciplinary research and collaboration required to probe the role of lipids and lipoproteins in disease. The biochemist, adult and pediatric clinician, cardiologist, epidemiologist, nutritionist, and biostatistician are all involved at various points and must integrate their experience to produce a comprehensive and lucid picture of lipid disorders, their community relevance, and their ultimate control.

Robert I. Levy, M.D.

Basil M. Rifkind, M.D.

Abbreviations

LDL	Low density lipoprotein
VLDL	Very low density lipoprotein
HDL	High density lipoprotein
IDL	Intermediate density lipoprotein
CHD	Coronary heart disease

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Lipoproteins and Lipid Transport: Structural and Functional Concepts

The plasma lipoproteins are macromolecular complexes that represent the functional unit for the transport of water-insoluble lipids in blood. Since Macheboeuf[1] first described these substances as "coenapse precipitated by acid," interest in and knowledge about them has evolved at a very rapid rate. The ultracentrifugal studies of Gofman et al.[2] in the late 1940s and early 1950s aroused new interest in the plasma lipoproteins. One major development was the observation concerning the relationship between high concentrations of the plasma lipoproteins and premature arteriosclerosis.[3] Another was the development of an improved method for the electrophoretic separation of plasma lipoproteins that depended upon the use of albuminated buffer.[4] Finally, the introduction of a simplified system for the classification of plasma lipoprotein phenotypes[5] created a world-wide interest in the diagnosis and definition of hyperlipidemias.

In this chapter we have placed emphasis on recent studies concerning the structure and metabolism of the plasma lipoproteins. Neither the review nor the bibliography are comprehensive; we have focused on contributions which appear to us to contain important new concepts concerning lipoprotein structure and function. More detailed discussions are available elsewhere.[6–8]

Supported in part by Grants HL-14194, HL-05435/34, and HL-17269-03 from the Department of Health, Education and Welfare. Richard L. Jackson and Joel D. Morrisett are Established Investigators of the American Heart Association.

NOMENCLATURE

We will define the plasma lipoproteins operationally on the basis of their rate of flotation in salt solutions in the ultracentrifuge.[2] The electrophoretic mobilities corresponding to these definitions are referred to below and are shown in Table 1-1. The plasma lipoproteins from normal subjects are usually divided into four major classes: chylomicrons, d < 0.95; very low density lipoproteins (VLDL), d 0.95–1.006; low density lipoproteins (LDL), d 1.019–1.063; and the high density lipoproteins (HDL), d 1.063–1.210. The lipoprotein fraction d 1.006–1.019 is referred to as intermediate density lipoproteins (IDL). In addition, HDL are usually subdivided into HDL_2, d 1.063–1.120, and HDL_3, d 1.120–1.210. The protein or apoprotein components of HDL are heterogeneous[10]. Various systems of apoprotein nomenclature exist; they should be considered only as provisional and not as uniformly accepted. For purposes of this review, we have adopted the A, B, C nomenclature (Table 1-1) for the apoproteins as suggested by Alaupovic.[9] According to this system, individual apoprotein families are designated apoA, apoB and apoC; there

Table 1-1
Composition and Properties of Human Plasma Lipoproteins

Properties	Chylomicrons	VLDL	LDL	HDL
Density	0.95	0.95–1.006	1.006–1.063	1.063–1.210
Electrophoretic mobility	Origin	Prebeta	Beta	Alpha
Major apoproteins	ApoB	ApoB	ApoB	ApoA-I
	ApoC-I	ApoC-I		ApoA-II
	ApoC-II	ApoC-II		
	ApoC-III	ApoC-III		
		Arginine rich		

is some disagreement concerning the heterogeneity of apoB at the present time. We should perhaps emphasize the point that in this review we are using the A, B, C system only to refer to apoproteins, not to families of lipoproteins, since there is some current disagreement as to whether any family of lipoproteins is limited to a discrete A, B, or C complement of apoprotein.

ApoA is the major class of proteins in HDL; they have also been described in chylomicrons. ApoB comprises virtually all of the protein of LDL and about 35–40 percent of the protein of VLDL. ApoC is the major apoprotein fraction of VLDL and makes up as much as 10 percent of the protein of HDL. Two other apoproteins for which we will use trivial names in this review are the "thin-line" protein, found in VLDL, LDL, and HDL, and the "arginine-rich" protein, found mainly in VLDL. The former has also been referred to by different laboratories as apoA-III or apoD. As new apoproteins are described, it would seem preferable to employ a trivial designation until it is firmly established to which of the apolipoprotein groups A, B, or C a protein belongs, or indeed whether the protein describes an entirely new class of apoproteins.

CHYLOMICRONS

Composition

The major function of the chylomicrons is the transport of dietary or exogenous triglycerides. Chylomicrons are synthesized in the intestine and traverse the lymphatic system to the thoracic duct, where they then enter the blood stream. Lymphatic chylomicrons contain, by weight, approximately 90 percent triglyceride, 5 percent phospholipid, 3 percent cholesterol and cholesteryl esters, and 2 percent protein.[11] The ratio of unesterified to esterified cholesterol is about 1. Phosphatidylcholine and sphingomyelin are the major phospholipids. Thoracic duct chylomicrons contain all of the apoprotein of VLDL.[12,13] In the study of Kostner and Holasek,[12] the approximate composition was 66 percent apoC, 22 percent apoB, and 12 percent apoA. Chylomicron particles range in diameter from 300 to 5000 Å; the larger the chylomicron particle, the greater the relative content of apoB.[13] When serum is added to intestinal chylomicrons, there is a transfer of apoC to these lipoproteins from HDL.[13,14]

Chylomicron synthesis and secretion occurs within the Golgi apparatus of the intestinal mucosa in a series of steps[15] which are briefly summarized. In the duodenum, the dietary triglycerides are hydrolyzed to 2-monoglycerides and free fatty acids. These products are thought to gain entry into the mucosal cells by the formation of micelles with conjugated bile salts.[16] Inside the mucosal cell, the fatty acids and monoglycerides are resynthesized into triglycerides, which are transported in the smooth endoplasmic reticulum. Chylomicron formation then occurs within the Golgi apparatus, from whence the lipoprotein particles are transferred to the lymphatic channels.

There has been a good deal of disagreement concerning the question of whether protein synthesis is required for the formation of intestinal chylomicrons.[17–22] While Sabestin and Isselbacher[17] initially reported that an inhibitor of protein synthesis blocked intestinal chylomicron formation in the rat, Redgrave and Zilversmit[18,19] subsequently attributed these effects to malabsorption and a decrease in lymph flow. In a reinvestigation of the subject, Glickman et al.[20,22] have reported that the protein synthesis inhibitor, acetoxycyclohexamide, causes an increase in chylomicron size and a decrease in the content of apoA-I. The strongest

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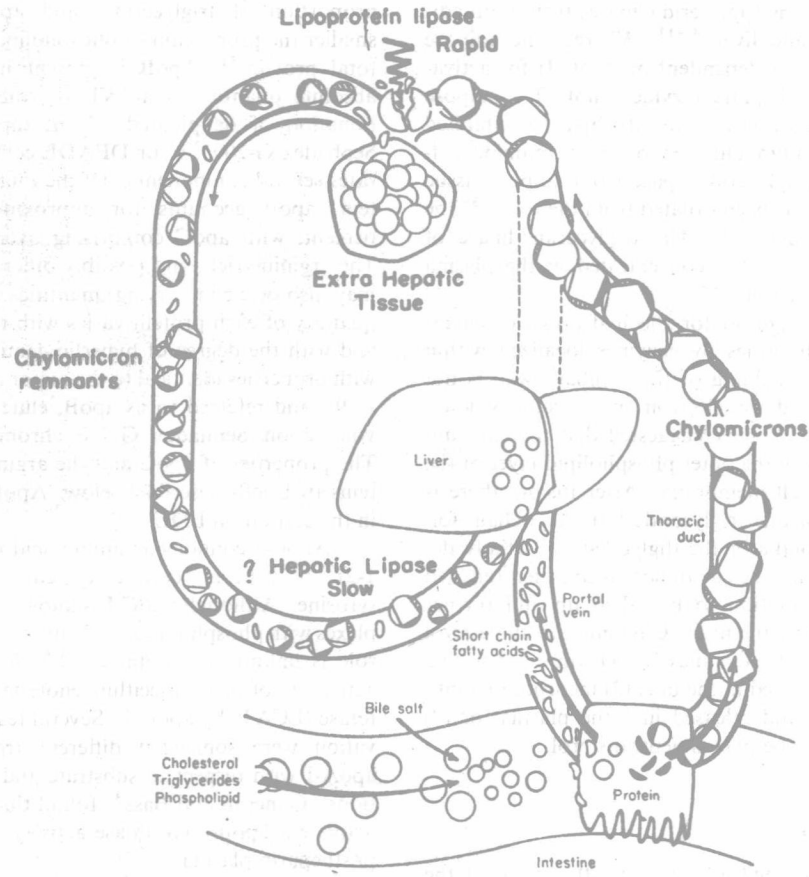

Fig. 1-1. A schematic representation for chylomicron metabolism. The scheme is modified from that suggested by Eisenberg and Levy.[6]

evidence relating protein synthesis to chylomicron formation comes from studies of the rare familial disorder, abetalipoproteinemia.[23] Patients with this disorder have fat malabsorption; apoB is completely absent from the plasma[24–26] and there are no circulating chylomicrons, VLDL, or LDL. It is likely that apoB formation is required for the synthesis and/or release of all of these classes of lipoproteins.

Catabolism

Chylomicrons are removed from the circulation faster than any of the other lipoprotein classes. In man, chylomicron triglycerides are removed in less than 1 hr.[27] Under normal conditions, chylomicron catabolism proceeds in two known phases (Fig. 1-1). In the first, triglycerides are hydrolyzed at extrahepatic tissue sites under the influence of a triglyceride lipase localized in the capillary endothelium. This process results in a relatively triglyceride-poor, cholesterol-rich remnant particle. In the second phase, the remnant particle is removed by the liver. Redgrave dissociated these two phases in the hepatectomized rat, which was still capable of hydrolyzing chylomicron triglycerides but could not remove the chylomicron remnant.[28]

In the first phase of chylomicron metabolism, unesterified fatty acids are released into the blood stream while the di- and monoglycerides are taken up in vacuoles and transported across the capillary wall for hydrolysis. Very little triglyceride lipase activity is present in the plasma of normal subjects. The enzyme is bound to the capillary endothelial cells in muscle and adipose tissue and can be released by intravenous administration of heparin. Triglyceride lipase activity is often referred to as postheparin lipolytic activity (PHLA). Postheparin

plasma contains triglyceride lipases from both adipose tissue and liver.[29–33] Whereas the adipose tissue enzyme is dependent on apoC-II for activation,[34–37] the hepatic enzyme is not. The adipose tissue lipase, but not the hepatic lipase, is inhibited by 1 *M* sodium chloride or by protamine sulfate.[34–37] Triglyceride lipase from adipose tissue and plasma has been isolated from the rat,[38,39] the pig,[40] and man.[41,42] The triglyceride lipase of hepatic origin[43,44] is concentrated in the plasma membrane fraction.[43]

The mechanism for the hydrolysis of chylomicron triglycerides by enzymes localized within the endothelial lining of the capillary wall is not known. Based on electron microscopic studies, Scow et al.[45–47] have suggested that the chylomicron fuses with the outer phospholipid layer of the endothelial cell membrane. After fusion, there is hydrolysis of one triglyceride fatty acyl chain followed by uptake of the diglyceride. Partially degraded or remnant chylomicrons are then released into the circulation to be taken up and further metabolized by the liver. Chylomicron cholesterol and cholesteryl esters may be (1) converted to bile acids and secreted in the bile, (2) incorporated into lipoproteins and released into the plasma, or (3) secreted into the bile as neutral sterol.

Structure

As mentioned above, over 90 percent of the chylomicron by weight is triglyceride. These water-insoluble lipids are maintained in a stable, emulsified form as they circulate in the blood stream. Most models for chylomicron structure have assumed that the neutral lipids are partially surrounded by an outer shell of phospholipid and protein.[48–50]

VERY LOW-DENSITY LIPOPROTEINS

Composition

An average preparation of VLDL contains 60–70 percent triglyceride, 10–15 percent phospholipid and cholesterol, and about 10 percent protein. Cholesterol and cholesteryl esters occur in a ratio of about 1:1 by weight. Sphingomyelin and phosphatidylcholine are the major phospholipids. The larger the size of a VLDL particle, the greater the proportion of triglycerides and apoC and the smaller the proportion of phospholipid, apoB, and total protein.[51] ApoB is present in a constant absolute quantity of all VLDL fractions. Fractionation of delipidated VLDL (apoVLDL) on Sephadex G-200[52,53] or DEADE cellulose[54] separates several components. Of the total VLDL protein, apoB accounts for approximately 30–35 percent, with apoC comprising over 50 percent. The arginine-rich, and possibly other apoproteins, may also occur in varying quantities. The relative quantity of each protein varies with the individual and with the degree of hyperlipidemia. A protein with properties identical to the major apoprotein of LDL, and referred to as apoB, elutes at the void volume on Sephadex G-200 chromatography.[55] The properties of apoC and the arginine-rich proteins are briefly described below. ApoB is described in the section on LDL.

ApoC-I contains 57 amino acid residues (Fig. 1-2)[56,57] with no cystine, cysteine, histidine, or tyrosine. Although apoC-I is known to form complexes with phospholipids,[58,59] its exact physiologic role is unknown. Soutar et al.[60] have described activation of plasma lecithin:cholesterol acyltransferase (LCAT) by apoC-I. Several features of activation were somewhat different from those of apoA-I with respect to substrate and other conditions. Ganesan and Bass[36] found that apoC-I will activate a lipoprotein lipase activity purified from postheparin plasma.

ApoC-II contains approximately 100 amino acid residues,[61] forms complexes with phospholipids similar to apoC-I and apoC-II,[59] and is a potent activator of lipoprotein lipase.[35–37] This protein plays an important role in lipoprotein metabolism by influencing the activity of lipoprotein lipase. As noted above, apoC-II activates adipose tissue but not hepatic triglyceride lipase.

ApoC-III is the most abundant and best studied of the apoC components. It contains 79 amino acid residues (Fig. 1-3) and is a single polypeptide chain.[62,63] To threonine residue 74 is attached a polysaccharide containing galactose, galactosamine, and either 0, 1, or 2 moles of sialic acid. The differing content of sialic acid accounts for the multiple electrophoretic mobilities of the apoprotein. ApoC-III avidly binds phospholipids[59,64–66] and has been reported to inhibit lipoprotein lipase.[67]

The arginine-rich protein was first isolated by Shore and Shore,[54] who found that, while the protein was present in all subjects studied, there were considerable variations in its concentration.

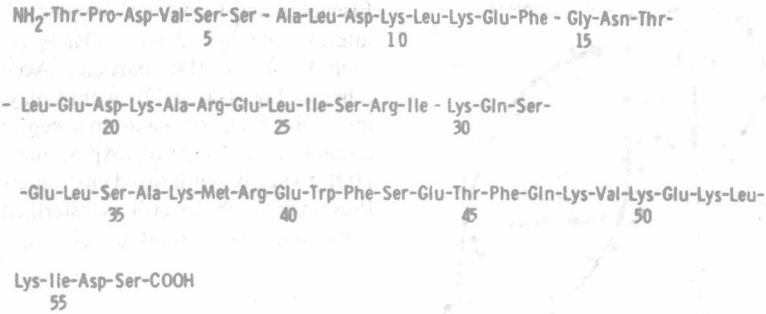

Fig. 1-2. The amino acid sequence of apoC-I. The sequence shown is that described by Jackson et al.[56] and Shulman et al.[57]

In normal subjects, the arginine-rich protein comprised about 17 percent of the total apoVLDL. Two laboratories have found that the concentration of this protein is increased in patients with type III hyperlipoproteinemia[54,68] or with hypothyroidism.[54,69] A similar protein has also been described in the VLDL of rabbits fed a cholesterol-rich diet.[70,71] Shelburne and Quarfordt[72] have reported that the arginine-rich protein from human VLDL has a molecular weight of about 33,000, amino-terminal lysine, and carboxyl-terminal alanine. The physiologic function of this protein and its relationship to cholesterol transport are potentially of great interest.

Synthesis

The liver and, to a lesser extent, the intestine are the sources of plasma VLDL.[73–78] At the present time, it is not possible to describe the sequence of the assembly process in which the apoproteins of VLDL are complexed with the various lipid constituents. It seems very likely, however, that the apoprotein moieties of VLDL are synthesized by ribosomes of the rough endoplasmic reticulum.[79] Lipoprotein particles isolated from the hepatic Golgi apparatus are quite similar in structure and composition to plasma VLDL.[79–81] VLDL from either intestinal lymph or an intestinal perfusate are devoid of apoC. In the presence of serum, the perfused rat liver secretes VLDL containing both apoB and apoC. Since apoC can be transferred between HDL and VLDL both in vivo and in vitro, it is not known whether VLDL is secreted from the liver with or without its full complement of apoC. Colchicine,[82,83] vincristine,[83] and orotic acid[84,85] inhibit VLDL secretion in the rat. Colchicine and vincristine are thought to block the microtubular system and, thus, the release of VLDL from the hepatocyte or Golgi apparatus. Orotic acid, on the other hand, is thought to block the final step of VLDL secretion by inhibiting the linkage of the carbohydrate to the apoproteins.[80,84,85]

Mechanisms regulating the overall synthesis of VLDL are poorly understood. Secretion of this class of lipoproteins undoubtedly is influenced by the availability of carbohydrate, of excess calories,

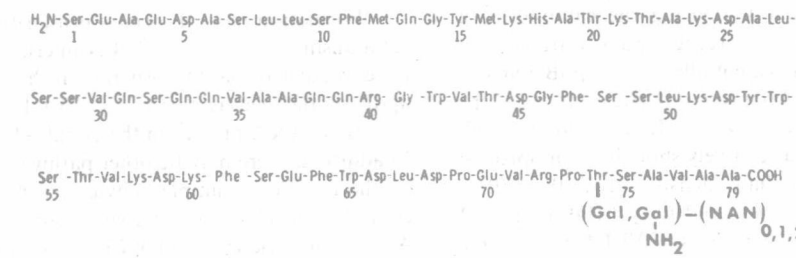

Fig. 1-3. The amino acid sequence of apoC-III. The sequence was determined by Brewer et al.[62,63] The carbohydrate moiety attached to threonine 74 contains one residue each of galactose (Gal) and galactosamine (Gal-NH_2) and either 0, 1, or 2 residues of N-acetylneuraminic acid (NAN).

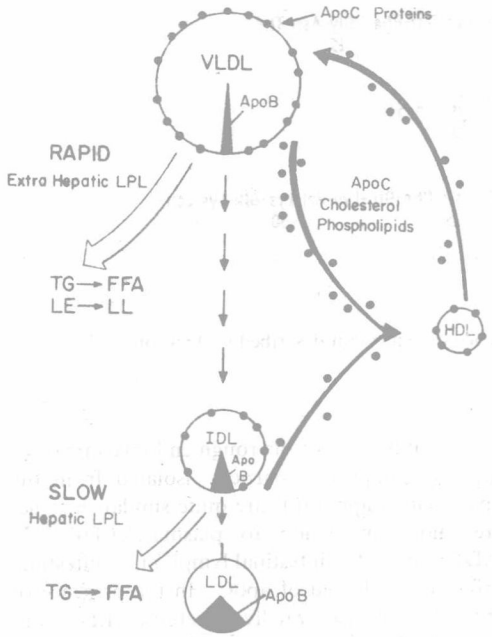

Fig. 1-4. A schematic representation for VLDL catabolism. The scheme is a modification of that suggested by Eisenberg and Levy.[6]

and of unesterified fatty acids of either endogenous or exogenous origin.[86–88] The nature of the available fatty acids is an important factor. For example, more VLDL triglyceride is secreted when the rat liver is perfused with oleic acid as compared with palmitic acid.[86]

Catabolism

The fate of VLDL triglycerides is thought to be similar to those from chylomicrons (See section on chylomicron catabolism). A suggested pathway for VLDL catabolism involving hydrolysis by extrahepatic tissues and subsequent hepatic uptake is shown in Figure 1-4. During the catabolism of VLDL, more than 90 percent of apoC is transferred to HDL, whereas essentially all of apoB remains with the original lipoprotein particle. In man, the transformation of VLDL → LDL occurs through the formation of a relatively short-lived lipoprotein (IDL) of intermediate density (d 1.006–1.019). According to Eisenberg and Levy,[6] IDL is formed very rapidly after hydrolysis of VLDL triglyceride by lipoprotein lipase. The mechanism of degradation of IDL to LDL is unknown. However, Eisenberg and Levy[6] have concluded that only one intermediate lipoprotein particle is formed from each VLDL or IDL particle. According to this scheme (Fig. 1-4), HDL would play an extremely important role, serving as an acceptor of apoC and unesterified cholesterol. ApoC may recycle from HDL to newly synthesized chylomicrons or VLDL. Presumably, cholesterol is esterified prior to its removal from the circulation.

LOW-DENSITY LIPOPROTEINS

Composition

LDL constitutes 40–50 percent of the plasma lipoprotein mass in man; its average concentration in normal adult American males is about 400 mg/dl and in females it is 340 mg/dl.[11] ApoB comprises approximately 25 percent by weight of LDL. The rest of the mass is made up of 50 percent cholesteryl esters, 30 percent phospholipids, 10 percent unesterified cholesterol, and 10 percent triglycerides. The major phospholipids are phosphatidylcholine (65 percent of the total) and sphingomyelin (25 percent). The major fatty acid is linoleic acid. By radioimmunoassay, all of the apoB in LDL can be identified,[89] and the concentration in normal subjects is 90 ± 24 mg/dl.[90] Technical problems in solubilizing and dissociating apoB have made progress in the characterization of this protein relatively slow as compared with the other apoproteins. Chemical modification and/or a chaotropic agent are usually required in order to obtain a soluble preparation.[91–96] Values for the molecular weight range from 8000 to 275,000, with 25,000–30,000 being the most common value reported.[8]

Synthesis

Formation of LDL occurs primarily from the catabolism of VLDL.[97–99] Eisenberg and Levy[6] have calculated that in normal man the amount of apoB synthesized as part of the VLDL equals the amount of apoB present in the circulation as LDL. In addition, there may be other pathways for LDL synthesis. For example, chylomicron remnants could be considered as a potential source of LDL. Also, the hepatic secretion of LDL is another potential source although currently there is no evidence to support such a pathway.

Catabolism

The sites and mechanism of LDL catabolism are not known. Degradation of radioactive LDL may be demonstrated in the perfused rat liver.[100] Sniderman et al.[101] have studied the rate of clearance of plasma LDL in the hepatectomized pig. Suprisingly, the half-life of LDL decreased from 19.3 to 9.5 hr after hepatectomy. This result would seem to imply that the liver does not serve as a major site of LDL removal. It may be hazardous, however, to generalize from the results with the hepatectomized pig. The recent publications of Goldstein and Brown, [102–108] however, do lend support to the occurrence of significant LDL catabolism by peripheral tissues. These workers have shown that fibroblasts from normal subjects in tissue culture contain specific receptors which bind LDL. As a consequence of this binding, cholesteryl ester and/or cholesterol are transferred to the cell, while LDL protein is catabolized. Furthermore, there is a repression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and an increased intracellular esterification of cholesterol. Of particular importance, these investigators observed that patients with familial type II hyperlipoproteinemia were either deficient in a specific LDL receptor or else the receptors were defective. Whether this receptor theory can account for the hypercholesterolemia in type II is an interesting possibility that merits further study.

Structure

Two models have been proposed for LDL structure based on small-angle x-ray scattering[109] or nuclear magnetic resonance spectroscopy.[110] By small-angle x-ray scattering, Mateu et al.[109] have observed outer and inner electron-dense regions that are separated by an intermediate low electron-dense region. They have assigned protein to both the inner and outer electron-dense regions. They have further suggested that the outer high electron-dense region contains a phospholipid bilayer. Both cholesterol and protein are assigned to the phospholipid bilayer. Finer et al.[110] have used nuclear magnetic resonance spectroscopy and have suggested that, instead of a bilayer structure, LDL consists of a trilayer in which the neutral lipids are packed between phospholipid fatty acyl chains. In this trilayer model, the protein is assigned to both the outer layer and an inner core. These investigators have also demonstrated that approximately 30 percent of the choline residues are immobilized and are not accessible to solvent. Obviously, further studies are needed to validate these bilayer or trilayer models or any other potential model of LDL structure.

HIGH-DENSITY LIPOPROTEINS

Composition

Approximately 50 percent of the HDL mass is protein; the other major constituents are cholesterol and cholesteryl esters (about 20 percent) and phospholipids (about 30 percent). Smaller amounts of triglycerides are present. HDL may be subfractionated by differential ultracentrifugation into HDL_2 and HDL_3;[111] the former are present in premenopausal women at about three times their concentration in men.[112] ApoA-I and Apo-II are the major proteins in HDL. ApoC and the thin-line protein are also present. The major phospholipid is phosphatidylcholine, comprising 70–80 percent of the total, with sphingomyelin making up 12–14 percent.

The amino acid sequence of apoA-I, the major protein of apoHDL, has been determined (Fig. 1-5).[113–115] This protein contains no cystine, cysteine, or isoleucine. The protein binds phospholipids and activates LCAT,[60,116] and it may play a role in regulating the content of membrane lipids.[117–119] ApoA-I appears to be the major HDL protein in all species studied to date.

ApoA-II from man contains two identical polypeptide chains of 77 amino acid residues each. The chains are linked by a single disulfide bond at residue 6 (Fig. 1-6).[120–122] Only the human and chimpanzee apoA-II have been found to contain dimeric structure.[123] In the baboon, rat, dog, rabbit, and cow, a monomeric structure is present. In the *Macacus rhesus* monkey, the cysteine at position 6 is replaced by a serine. The presence of a disulfide structure does not appear to be essential for lipid binding. The physiologic function of apoA-II is unknown.

The thin-line protein,[124] also referred to as apoD[125] or apoA-III,[126] comprises approximately 1 percent of human apoHDL. The estimated molecular weight of this protein is 20,000.[127] Kostner has reported that the thin-line protein activates LCAT.[127]

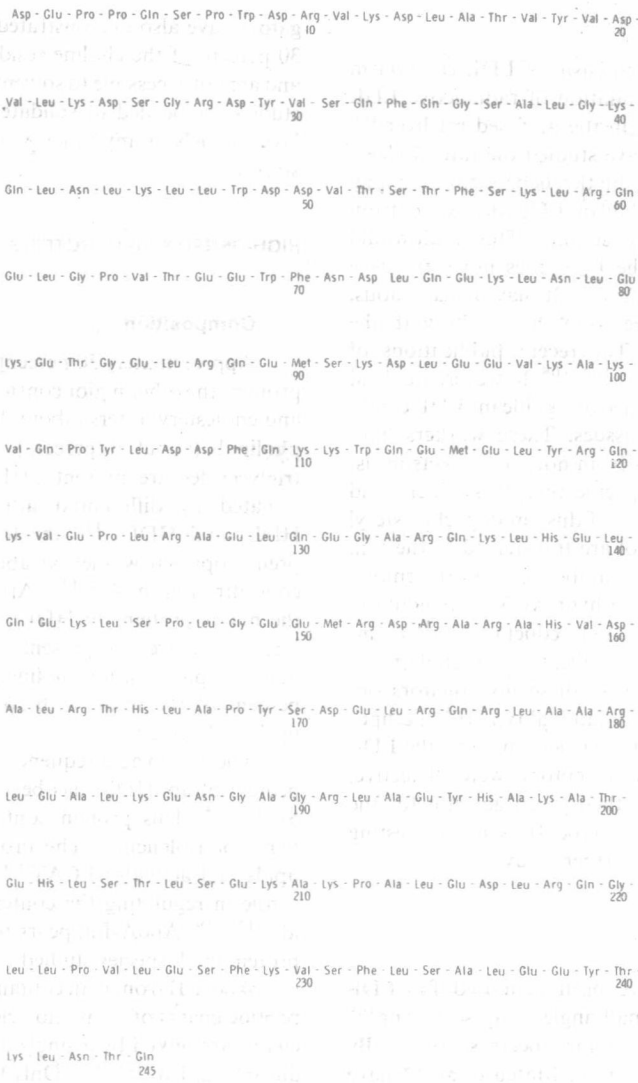

Fig. 1-5. The amino acid sequence of human high-density apolipoprotein apoA-I as described by Baker et al.[113]

Synthesis

Most available information concerning HDL synthesis comes from studies with the rat. Direct evidence for HDL synthesis has been obtained from prefused rate liver experiments.[74,78,128] The HDL of hepatic origin contains both apoA and apoC, while intestinal HDL contains only apoA. Inhibition of LCAT activity in a perfused liver preparation results in the formation of discrete particles which form rouleaux.[79] These particles have an edge thickness of 46 Å and a diameter of about 190 Å. They contain primarily phospholipid, protein, and unesterified cholesterol. Hamilton and Kayden[129] have suggested that they represent precursors of normal spherically shaped HDL. The discs would represent a phospholipid bilayer, which presumably could be converted to a spherical particle through the esterification of cholesterol catalyzed by plasma LCAT. Since apoA-I activates LCAT, these investigators have suggested that the enzyme binds to the nascent HDL through a specific interaction and

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