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THE HYPOBETALIPOPROTEINEMIAS

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CONTENTS

ABSTRACT

The fifth- and ninety-fifth-percentile concentrations of low-density lipoprotein (LDL) cholesterol in most Western populations are approximately 90 and 200 mg/dl, respectively. Persons with LDL cholesterol levels equal to or less than the fifth percentile are defined as having hypobetalipoproteinemia. Epidemiologic studies show that such individuals have lower-than-average risk for atherosclerotic cardiovascular disease but higher risk for a variety of cancers, pulmonary, and gastrointestinal diseases than persons with higher levels of cholesterol. The reasons for this are not known, nor are the causes of most cases of hypobetalipoproteinemia. However, in some well-studied kindreds the hypobetalipoproteinemia phenotype is inherited as an autosomal dominant trait. Heterozygotes in such kindreds are usually healthy and have no difficulty absorbing dietary fat. In most kindreds, the molecular

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variants responsible for the hypobetalipoproteinemia are unknown, but a subset of kindreds have strong genetic linkages between the low-cholesterol phenotype and truncation-producing mutations of the apolipoprotein (apo) B–100 gene.

The truncations of apoB are named according to a centile nomenclature. The full-length 4536–amino acid protein is called apoB-100, and the 25 truncations identified to date have been named apoB-2 to apoB-89. The mutations introduce premature termination codons resulting from frameshift-producing base additions or deletions. The mutations produce slowed rates of secretion of the truncated apoBs relative to the apoB-100s present in the heterozygotes. In addition, the apoB-100 molecules of the heterozygotes are also secreted at rates slower than those observed in closely matched normolipidemic controls. These physiologic results account for the hypobetalipoproteinemia of these subjects. The response of the plasma lipoproteins of heterozygotes to the manipulation of various dietary components remains to be determined. Additional low-cholesterol syndromes are autosomal recessive forms of hypobetalipoproteinemia, chylomicron retention disease, and abetalipoproteinemia. The molecular causes of the first two are unknown. Abetalipoproteinemia is an autosomal recessive condition resulting from mutations of the microsomal triglyceride transfer protein. All three conditions are characterized by vanishingly small concentrations of LDL, dietary fat malabsorption, and failure to thrive in infancy.

INTRODUCTION

Subjects with hypobetalipoproteinemia (HBL) are defined as those with low-density lipoprotein (LDL) cholesterol in the lowest fifth percentile. Three well-described inherited syndromes comprise a subset of HBL subjects. The first is familial HBL (FHBL), which segregates as a Mendelian dominant condition. The second and third are abetalipoproteinemia (ABL) and chylomicron-retention disease (CRD), both of which segregate as Mendelian recessives. The molecular defects underlying the majority of FHBL cases are not known; however, a few cases have been linked to apolipoprotein B–100 (apoB-100), some of which are associated with truncation-producing mutations of apoB-100. The defective molecule in ABL is the microsomal triglyceride transfer protein (MTP), a heterodimeric protein coupled to the enzyme protein disulfide isomerase in the endoplasmic reticulum. The molecular etiology of CRD has not been identified.

Apolipoprotein B–100

The full-length apoB–100 (39, 52) is comprised of 4536 amino acids and is a major transporter of lipids in plasma. It is secreted as an integral part of very

low-density lipoprotein (VLDL) particles from liver and is retained in VLDL throughout its metabolic transformations and clearance from plasma. A major function of VLDLs is to deliver liver-derived triglycerides to peripheral tissues. As VLDLs circulate, they transiently adhere to glycosaminoglycan molecules on endothelial cells (19, 50), where they encounter lipoprotein lipase and hepatic lipase, enzymes that catalyze the hydrolysis of VLDL triglycerides to form free fatty acids and glycerol. Peripheral tissues utilize both the resulting diet-derived fatty acids and the glycerol. During triglyceride depletion, VLDL particles are converted first to intermediate density lipoprotein (IDL), then to LDL. Having performed their lipid-transporting function, most apoB-100-containing particles are cleared from plasma as LDLs, but some are cleared at the IDL stage, before they are completely depleted of triglycerides. LDLs are removed from plasma via LDL receptor–mediated endocytosis (7); under normal conditions, approximately 70% of LDLs are removed by hepatic LDL receptors, and the rest are cleared by LDL receptors in other tissues.

Apolipoprotein B–48

The other form of apoB found in plasma is apoB-48, which is secreted by enterocytes as an integral protein of chylomicrons. ApoB-48 is identical to 48% of the amino-terminal portion of apoB-100 and is the translation product of apoB-100 mRNA edited at amino acid position 2152 to form a termination codon (8, 34). The editing enzyme is a cytidine deaminase that converts cytidine to uridine. The metabolism of apoB-48 strongly resembles that of apoB-100. ApoB-48 accompanies chylomicron particles throughout their metabolic lives as they deliver their diet-derived triglycerides to peripheral tissues and are converted to chylomicron remnants in the process. These remnants are in turn cleared from plasma not by LDL receptors—apoB-48 does not possess the LDL receptor–recognition domain—but by remnant receptors (3, 16, 18, 27). Remnants are recognized by remnant receptors via apoE (11), another protein component of remnants. Molecular defects in apoB-48 have not been directly implicated in any of the HBL syndromes.

Apolipoprotein B Metabolism

Levels of VLDL and chylomicrons, the secreted lipoproteins, are determined by rates of secretion relative to rates of conversion to IDL and remnants, respectively (4). Levels of IDL are determined by rates of conversion from VLDL, rates of removal from plasma as IDL, and rates of conversion to LDL. Finally, levels of LDL and chylomicron remnants are functions of rates of conversion from IDL and chylomicrons, respectively, and of rates of clearance via receptor-mediated endocytosis.

The secretion of apoB from either liver or intestinal cells is regulated by the amount of lipid available for transport. For example, when hepatocytes

take up increasing amount of fatty acids, they esterify increasing amounts of these fatty acids into triglycerides (and cholesterol esters and phospholipids) and assemble and secrete greater numbers of larger-than-usual triglyceride-enriched VLDL particles containing one molecule of apoB-100 per particle (32). The increased secretion of apoB-100 is not accompanied by increased de novo synthesis of apoB-100 molecules. Rather, the rate of synthesis remains constant, as does the number of apoB-100 mRNA molecules per cell (28, 35). The increased secretion results from the diversion of larger proportions of newly synthesized apoB-100 molecules away from an intracellular degradation pathway in the endoplasmic reticulum in favor of the secretory pathway that carries the VLDL particles through the Golgi apparatus and secretory vesicles and out of the cells (11). In other words, the regulation of hepatic secretion of apoB-100 by nutritional components seems to occur at posttranslational sites. Regulation of secretion of apoB-100 by thyroid hormone and estrogen may entail changes in rates of its synthesis (42). The molecular basis for the regulation of secretion of intestinal apoB-48 is unknown.

The intravascular metabolism of apoB-100 and apoB-48-containing lipoproteins also depends on lipoprotein lipase and hepatic lipase–catalyzed rates of conversion of VLDL, IDL, and chylomicrons to LDL and remnants, respectively. The activities of both enzymes are regulated by hormones and metabolic states, e.g. by fasting and feeding, by exercise, and by steroid and thyroid hormones (39). Finally, rates of IDL and LDL clearance depend on intact, functional LDL receptors whose activities are also regulated by dietary (43) and hormonal (42) factors and are inversely related to the availability of intracellular cholesterol (7). Further metabolism of chylomicron remnants also requires the functional activities of remnant receptors (3, 18). The potential for genetic regulation of these pathways is enormous because there are a large number of proteins involved, and each is subject to genetic variation of structure and regulation. I confine my discussion to the molecules implicated in the low-cholesterol syndromes.

MOLECULAR DEFECTS OF apoB AND DYSLIPOPROTEINEMIA

Familial Hypobetalipoproteinemia and Truncations of apoB-100

In kindreds with familial hypobetalipoproteinemia (FHBL, LDL cholesterol in the lowest fifth percentile for homozygotes and in the lowest tenth percentile in heterozygotes) (17), the phenotype segregates as a autosomal codominant trait. Levels of VLDL and high-density lipoprotein (HDL) are usually normal. The molecular defects and genetic etiologies of FHBL in most kindreds are

Table 1 Truncation mutations of apoB (St. Louis)

Truncation	DNA Mutation	Mutant Protein
B 38.9	−C bp 5444	22 new $AAs_{1744} \rightarrow Stop_{1767}$
B 40	−TG bp 5693–5694	$Val_{1829} \rightarrow Cys_{1829} \rightarrow Stop_{1830}$
B 52	−TTAAG bp 7276–7283	5 new $AAs_{2356} \rightarrow Stop_{2362}$
B 54.8	C → T 7665	$Arg_{2486} \rightarrow Stop_{2486}$
B 70.5	+A 9754–9760	13 new $AAs_{3183} \rightarrow Stop_{3197}$
B 75	−C 10366	$Thr_{3386} \rightarrow Met_{3386} \rightarrow Stop_{3387}$
B 89	−G 12309	6 new $AAs_{4033} \rightarrow Stop_{4040}$

unknown, but in some the FHBL syndrome is clearly associated with variant forms of the apoB gene. Of these, the most readily identifiable subset consists of mutations that specify the translation of truncated forms of apoB (Table 1). Most of the research has concentrated on these truncation mutations (12).

Probands containing apoB truncations are identified by screening subjects with low-cholesterol levels (Table 2). ApoB is isolated from plasma by immunoprecipitation, separated from other proteins on sodium dodecyl sulfate (SDS) gels, and visualized by immunoblotting. Alternatively, lipoproteins are separated on SDS gels and silver-stained. Truncations are named according to a widely used nomenclature for apoB. ApoB-100 has a molecular weight of 4536 amino acids, and the molecular weight of apoB-48 is 48% of that of

Table 2 Lipoprotein lipids of hypobeta kindreds

ApoB alleles (dl^{-1})	TCHOL (mg/dl^{-1})	TG (mg/dl^{-1})	LDL-C (mg/dl^{-1})	HDL-C (mg/dl^{-1})	ApoB (mg/dl^{-1})
Subjects with truncated forms of apoB					
B89/B40 (3)[a]	70 ± 4	84 ± 37	15 ± 5	40 ± 10	18 ± 7
B40/B100 (1)	108	72	49	45	29
B89/B100 (2)	139 ± 26	102 ± 12	78 ± 19	40 ± 9	81
B38.9/B100 (7)	111 ± 27	56 ± 26	49 ± 12	52 ± 16	36 ± 9
B40/B100 (2)	103 ± 15	118 ± 4	36 ± 18	44 ± 4	43 ± 10
B52/B100 (11)	114 ± 28	59 ± 38	46 ± 21	54 ± 13	47 ± 25
B54.8/B100 (11)	123 ± 20	69 ± 24	49 ± 14	60 ± 15	26 ± 8
B70.5/B100 (2)	119 ± 16	98 ± 17	46 ± 8	54 ± 12	41 ± 1
B75/B100 (4)	115 ± 14	92 ± 50	48 ± 11	49 ± 4	28 ± 9
Relatives with wild-type apoB					
B100/B100 (44)	189 ± 38	155 ± 100	107 ± 32	50 ± 12	91 ± 32

[a] Mean ± SD ( ) = number of subjects.

apoB-100. Truncations identified to date range in size from apoB-2 to apoB-89. Techniques of molecular genetics such as restriction digestions, Southern blotting, polymerase chain reaction (PCR), subcloning, and DNA sequencing are used to characterize genetic defects. These defects include frameshifts caused by base additions or deletions; base substitutions within exons that result in premature stop codons; small deletions at intron-exon junctions presumably due to defective mRNA splicing; and much longer deletions (12–15, 25, 44–46, 49, 53).

Tissue Sources of Truncated ApoB

ApoB is primarily produced either in hepatocytes or in enterocytes. To ascertain which tissue produced the truncations, investigators incubated small intestinal biopsies with ^{35}S-methionine, followed by immunoprecipitation and SDS-gel electrophoresis. Truncations shorter than apoB-48 were synthesized in small intestine; longer truncations were not, probably because the apoB-100 mRNA editing enzyme edits both the normal and the mutant apoB mRNAs. Thus, truncations shorter than apoB-48 are likely to be produced in intestine, whereas longer truncations are not (23). The liver is the other source of apoB in plasma. Because it contains no apoB mRNA editing activity, it likely produces both apoB-100 and truncated apoBs of all sizes.

Metabolism of Truncated ApoB

Metabolic studies were performed in heterozygotes with truncated apoB and in controls homozygous for apoB-100. [^{13}C] leucine was infused intravenously for 8 h, and venous blood samples were collected for up to 120 h. ApoB-100 and truncated apoB were isolated from plasma lipoproteins and hydrolyzed, and the resulting ^{12}C- and ^{13}C-labeled leucines were separated by ion exchange chromatography. Leucines were quantified by negative ionization, selective ion detection gas chromatography mass spectrometry. Kinetic parameters were calculated using CONSAM/SAAM multicompartmental, computer-based kinetic models (4). These kinetic models are widely used in lipoprotein metabolic studies. They use differential equations and fit the data points to the kinetic model. Fit is tested by statistical techniques. All truncated forms were produced at lower rates than their normal apoB-100 counterparts in the same heterozygous subjects. Reductions ranged from 15% of apoB-100 production for apoB-89 to 85% for apoB-40; relative production rate was related directly to size of the truncated apoB. Thus, diminished production of truncated apoB may explain, at least in part, the lower LDL and apoB levels in heterozygotes (29, 30).

Fractional catabolic rates (FCRs) of the apoB-75 and apoB-89 truncations were higher than those of apoB-100 in the same subjects. Both of these truncations (22, 30) contain the LDL receptor–recognition domain, as does

normal apoB-100. The enhanced FCRs suggested that truncated apoB with these longer sizes may exhibit enhanced binding to the LDL receptor. Indeed, experiments in rabbits (31) and in cultured human fibroblasts (21, 22) confirmed these findings and suggested that the C-terminal region of apoB-100 may normally modulate the accessibility of the LDL receptor domain, thereby altering the affinity of LDL to its receptor. In shorter forms of truncated apoB (<apoB-71), the domain has been deleted. FCRs of the shorter forms of truncated apoB are also altered to varying degrees, but the magnitudes of the changes appear too small to account for the very low levels of apoB in these patients. The percentage of VLDL converted to IDL and LDL in these studies was the same for lipoproteins containing apoB-100 and for those containing truncated forms of apoB, suggesting that the removal of lipids from VLDL and IDL is not affected in the lipoproteins containing truncated forms of apoB.

ApoB-100, the product of the normal allele, was produced at a lower rate in patients that were heterozygous for FHBL and containing truncated apoB than in control subjects that were normolipidemic and were closely matched for apoB-100 and apoB-100 phenotype (1). This was an unexpected finding. Thus, the low levels of total apoB in heterozygotes with truncated apoB appear to result from low rates of production of both the truncated and full-length forms of apoB.

Our heterozygous FHBL subjects are usually asymptomatic and able to absorb dietary fat in a normal manner (2). It is not known how and to what extent the plasma lipoproteins of FHBL heterozygous subjects are affected by dietary manipulations of fat, cholesterol, or other macronutrients over longer periods of time, since no formal studies are available. In contrast, the homozygous or compound heterozygous forms of FHBL are more serious conditions. These patients may have fat malabsorption and vanishingly low to undetectable levels of plasma apoB-100, and some may fail to thrive as infants and small children. In sum, they may resemble subjects with abetalipoproteinemia (36).

The prevalence and incidence of common chronic diseases in FHBL subjects have not been determined because no formal epidemiologic studies are available in FHBL populations. Anecdotal data collected from our kindreds suggest that the prevalence of atherosclerotic disease may be low, but this impression needs formal confirmation.

Familial Defective apoB

Hyperlipoproteinemia is not the primary topic of this review. For the sake of completeness, however, I include a brief description of the apoB 3500 mutation of apoB-100, which produces a syndrome similar to autosomal codominant familial hypercholesterolemia (FH). Whereas "classical" FH results from any one of more than 100 mutations of the LDL receptor gene, the FH-like phenotype is caused by the apoB defect and is called familial defective apoB

(FDB). Patients heterozygous for FDB manifest a range of symptoms, with LDL cholesterol levels ranging from approximately 160 mg/dl, with no clinical signs of hypercholesterolemia per se (although coronary heart disease may be present), to LDL cholesterols >300mg/dl, accompanied by xanthomatosis and severe premature coronary heart disease (9, 10). Patients homozygous for FDB or heterozygous for both FH and FDB manifest more severe signs and symptoms. The FDB-producing mutation substitutes a glutamine for an arginine at amino acid position 3500, rendering apoB-100 nearly unrecognizable by normal LDL receptors and causing LDL to accumulate in plasma. However, the factors responsible for variations in severity of the heterozygous phenotype in various kindreds or individuals have not been identified. Other amino acid substitutions at the same site likely produce a similar phenotype.

Abetalipoproteinemia

In this syndrome, signs and symptoms of intestinal malabsorption and failure to thrive are apparent in infancy. If these infants are not treated with large doses of fat-soluble vitamins, in particular tocopherol, signs of CNS disease and retinal degeneration appear early in life. Over several years, untreated abetalipoproteinemia (ABL) gradually leads to increased incapacity, a wheelchair-bound existence, and eventual death in the early teens (6, 36, 48). Large doses of tocopherol prevent or halt the progression of most clinical deterioration in these patients (5, 26, 38).

ABL results from a nearly complete inability to assemble and secrete either intestinal chylomicrons or hepatic VLDL particles despite the ability to synthesize intact lipid and apoprotein and in the accumulation of partially assembled lipoproteins in the endoplasmic reticulum (ER) of enterocytes and probably hepatocytes as well. The overall result is the near absence of apoB-containing lipoproteins in plasma (24, 36). The molecular defect resides in the large subunit of the microsomal triglyceride transfer protein (Table 3) (24, 40, 41, 51), a protein homologous to chicken vitellogenin, which is important in

Table 3 Mutations in the mtp gene linked to abetalipoproteinemia

Type of mutation	Site	MT protein[a]	Reference
Splice site	+91 bp (mt 1867–1868)		41
Frameshift	−C bp 215	78aa b236 stop	40
Nonsense	C → T bp 178	594aa Arg → stop	40

[a] Normal MTP large subunit has 894aa (~100 kDa).

assembly of egg-yolk lipoproteins (40). MTP is thought to perform an analogous function vis-à-vis chylomicron and VLDL assembly, perhaps moving lipids from sites of synthesis in ER membranes to nascent apoB-containing lipoproteins in ER lumen. Three genetic defects have been identified: one frameshift and one nonsense mutation, both of which are predicted to result in truncated nonfunctional proteins, and a splice-site mutation resulting in a nonspliced mRNA.

Chylomicron Retention Disease

This syndrome resembles ABL symptomatically with respect to dietary fat malabsorption and its consequences (37, 49). However, examination of plasma reveals apoB-100-containing particles but no apoB-48-containing particles. The intestinal transcription of apoB-100 mRNA and its editing to apoB-48 mRNA appear to proceed at normal rates, and both apoB and dietary triglycerides are detected in enterocytes, suggesting that enterocytes can synthesize elements of chylomicrons. Nevertheless, chylomicrons are not secreted. The molecular defect is unknown but does not appear to be related to apoB (33).

Isolated Vitamin E Deficiency

Symptomatically, patients with vitamin E deficiency have neurologic and visual impairments similar to those seen in ALP and CRD, but their plasmas contain apoB, and the concentrations of the related lipoproteins are near normal (47). The defect seems to lie not in malabsorption of vitamin E from the intestine but rather in an inability to incorporate vitamin E into lipoproteins in liver owing to a defective hepatic vitamin E–binding protein. This hepatic defect results in deficient transport of vitamin E to peripheral tissues (20, 52).

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