ApoB Metabolism in Familial Hypercholesterolemia

Inconsistencies With the LDL Receptor Paradigm

Waldo R. Fisher, Loren A. Zech, Peter W. Stacpoole

Abstract

The biology of the low-density lipoprotein (LDL) receptor has been examined in detail, and a paradigm for LDL metabolism has evolved from comparative studies of cholesterol metabolism in a variety of cells cultured from normal individuals and subjects with familial hypercholesterolemia (FH). Cultured cells from patients with homozygous FH lack a functional LDL receptor and show diminished LDL clearance, induction of the enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, increased cholesterol synthesis, decreased cholesterol ester production, and depleted cholesterol ester stores. The observed decrease in the fractional catabolic rate (FCR) of LDL is attributed to the mutated LDL receptor gene. However, in the experimental animal model of this disease, the Watanabe heritable hyperlipidemic (WHHL) rabbit, cholesterol ester stores are increased, while hepatic cholesterol synthesis is decreased, and the LDL apolipoprotein (apo) B production rate is increased in patients with FH. These findings raise questions about the adequacy of the paradigm in understanding hepatic cholesterol metabolism in vivo. In humans, apoB metabolism is believed to be principally determined by the liver, where apoB is both synthesized and catabolized. Assuming the neutral lipid content of the liver is the major determinant of apoB metabolism, we postulated that the changes in apoB metabolism in FH are predictable when based on the assumption of an increase in hepatic cholesterol and cholesterol ester content, as observed both in the WHHL rabbit and in humans. We examined this hypothesis in vivo in patients with heterozygous FH by using tracer kinetic methodology and have used similar data from normal and hypertriglyceridemic (HTG) subjects as controls. Whereas normal and HTG subjects secrete apoB primarily as large, triglyceride-enriched very-low-density lipoprotein (VLDL), heterozygous FH patients have an absolute decrease in apoB production and secrete almost 40% of apoB as smaller intermediate-density lipoprotein (IDL)/LDL. In normal humans, about half of secreted apoB is catabolized rather than being converted to LDL. In HTG subjects two thirds of apoB follows this same route, by which VLDL remnants remaining after triglyceride hydrolysis are largely returned to the liver. In contrast, in FH subjects secreted apoB is fully converted to LDL. Thus, although total apoB secretion is reduced in FH subjects, total LDL production is greater than in either normal or HTG subjects. Under basal conditions the elevated LDL in heterozygous FH is due to both decreased LDL receptor-mediated catabolism and increased LDL production. However, the number of LDL receptors actually expressed is suppressed below the number of potentially functional receptors. Support for this conclusion is derived from the findings that when diets or drugs are administered that decrease the hepatic concentration of cholesterol esters, the FCR of LDL increases to normal values, reflecting an increase in expressed hepatic LDL receptors. Apparently in heterozygous patients these receptors are normally suppressed below the upper limit that can be expressed by a single functional gene. In summary, three major changes occur in apoB metabolism in heterozygous FH subjects: (1) a decrease in total and VLDL apoB secretion with a shift to the production of smaller IDL/LDL species; (2) the loss of the catabolic pathway for VLDL apoB remnants; and (3) a reversible decrease in the FCR of LDL apoB, which is normalized by dietary or drug perturbations that reduce hepatic cholesterol. All these findings are explainable as an adaptation to an increase in hepatic cholesterol ester content but not by the classic LDL receptor paradigm. How this pathophysiology arises from the mutation of the LDL receptor gene is unknown. (Arterioscler Thromb. 1994;14:501-510.)

Key Words • apolipoprotein B • LDL • familial hypercholesterolemia • compartmental modeling • LDL receptor • cholesterol esters

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From the Departments of Medicine (Endocrinology and Metabolism) and Biochemistry and Molecular Biology (W.R.F., P.W.S.), University of Florida, College of Medicine, Gainesville, and the Laboratory of Mathematical Biology (L.A.Z.), National Institutes of Health, Bethesda, Md.

Correspondence to Dr Waldo R. Fisher, Box 100226 JHMHC, University of Florida College of Medicine, Gainesville, FL 32610.
overproduction as well as underutilization of LDL may contribute to the hypercholesterolemia.

Second, hepatic cholesterol ester content is increased. The livers of Watanabe heritable hyperlipidemic (WHHL) rabbits, an animal model of FH, have a modest increase in free cholesterol but a threefold increase in cholesterol ester content. Moreover, newly secreted very-low-density lipoprotein (VLDL) from perfused livers of WHHL rabbits is enriched threefold in cholesterol esters, suggesting that increased hepatic uptake of cholesterol-rich lipoproteins occurs in these animals. In humans, a single report of liver biopsies obtained from two patients with homozygous FH demonstrated increases of 53% and 129% in total cholesterol compared with that found in the livers of normocholesterolemic individuals, and most of the increase in cholesterol content was due to cholesterol esters.

Third, cholesterol synthesis and HMG-CoA reductase activity apparently are suppressed. Thus, cholesterol synthesis is depressed in the livers of WHHL rabbits. In addition, HMG-CoA reductase activity and mass are reduced in circulating mononuclear cells isolated from human FH heterozygotes and are further decreased in homozygotes. These apparent inconsistencies with the LDL receptor paradigm justify a reexamination of the pathophysiology of hypercholesterolemia in FH.

Davis et al postulate that the neutral lipid composition of the hepatocyte determines the lipid composition of secreted lipoproteins. If so, then plasma apolipoprotein (apo) B metabolism in FH may be regulated in a manner consistent with the reported increase in hepatic cholesterol ester content. We tested this hypothesis by reexamining published kinetic data on human apoB metabolism; this report presents the results of this analysis.

**ApoB Secretion**

The current understanding of apoB secretion has been the subject of three recent reviews that examine apoB synthesis and secretion at the cellular level and in intact physiological systems. It is believed that only a portion of synthesized apoB is secreted while the rest is degraded, and the availability of fatty acids as triglyceride precursors appears to be a prime determinant of apoB secretion. Channeling of apoB secretion into large VLDL, VLDL/IDL, and LDL has been demonstrated in vitro. In HepG2 hepatoma cells, apoB is predominantly secreted as LDL but shifts to larger, VLDL-like particles when fatty acids are provided to the cells. In the perfused liver and in rat hepatocytes, VLDL is the predominant apoB particle secreted, but the size, density, and lipid content of the particle may vary depending on the availability of triglyceride and cholesterol to the hepatocyte.

Studies in human subjects describe the secretion of apoB in particles ranging in size from large VLDL to small LDL. The mix of apoB particles secreted differs among the acquired or congenital disorders of apolipoprotein metabolism and can be influenced by dietary nutrients.

In contrast to radioiodinated apoB-containing tracers, the use of [3H]leucine, an endogenously incorporated tracer, permits direct examination of the secretion of apoB in humans and quantification of early events in the secretion and metabolism of apoB-containing lipoproteins. Fig 1 summarizes results on apoB secretion rates, using [3H]leucine, in three groups of subjects, each of which was studied under similar protocols. Total apoB secretion is increased in patients with hypertriglyceridemia (HTG) compared with healthy control subjects and particularly compared with patients with FH.* In addition, both normal and HTG individuals secrete most apoB as triglyceride-rich VLDL. In FH, however, almost 40% of apoB is secreted as smaller, IDL/LDL-sized particles. These observations reinforce similar findings that involved radioiodinated apoB tracers. Taken together, the kinetic observations support the premise that the large triglyceride load exported from the liver in HTG determines the increased secretion of apoB as VLDL. In FH subjects, triglyceride transport appears to be a lesser function of apoB, as shown both by the mean VLDL apoB secretory rate (14 mg/kg per day) that is less than half the secretory rate for normal (32 mg/kg per day) and HTG (52 mg/kg per day) individuals (Fig 1) and by the common occurrence of normal or low triglyceride concentrations in FH patients. We interpret these results as being consistent with the hypothesis of Davis et al that the hepatic triglyceride load is the primary determinant of VLDL apoB secretion both in normal subjects and HTG patients. Thus, in FH subjects an increase in hepatic cholesterol ester content is accompanied by a decreased secretion of both VLDL and apoB, and a larger portion of apoB appears in plasma as smaller particles in which cholesterol esters are the predominant core lipid.

The [3H]leucine tracer is particularly useful in demonstrating metabolic channeling of apoB because it distinguishes apoB secreted as large VLDL that is sequentially delipidated to LDL via the delipidation pathway from smaller secreted particles that are rapidly metabolized to LDL (the IDL pathway). Using this technique, the HTG patients each had an isolated hypertriglyceridemia, but data were not available to differentiate between familial hypertriglyceridemia and familial combined hyperlipoproteinemia.
capability, the importance of the neutral lipid content of the liver in determining the secretion of apoB as either large VLDL- or IDL/LDL-sized particles was investigated in FH subjects by perturbing the hepatic lipid content through dietary manipulation. It is well recognized that a diet high in carbohydrates results in an increased triglyceride content of VLDL, and the consequences of such a perturbation on apoB metabolism have been investigated by kinetic studies in normal and HTG subjects. Our FH subjects were first fed a control diet of 45% carbohydrate and 40% fat followed by a 90% carbohydrate, 1% fat diet. While consuming the control diet, these subjects secreted 78% of their apoB by the IDL pathway and the remainder by the delipidation pathway. When an increase in hepatic triglyceride production was induced by switching to the high-carbohydrate, low-fat diet, the secretion of apoB by the IDL pathway fell from 78% to 22%, and triglyceride-rich VLDL became the major form in which apoB was secreted; however, net apoB production did not change.

Thus, in the FH subjects the response to a high-carbohydrate diet is similar to that in normal and HTG individuals: total apoB secretion does not increase appreciably, but the secreted particles become enriched in triglycerides. However, under basal conditions, in FH a larger proportion of secreted apoB is in the form of smaller, relatively cholesterol-enriched particles.

**VLDL Remnant Metabolism**

Metabolic channeling is a feature of apoB metabolism, which, though readily recognized with the use of endogenously incorporated tracers such as [3H]leucine, is also observed with radioiodinated apoB tracers. ApoB secreted as large VLDL and metabolized by the delipidation pathway may be removed from plasma as small VLDL and its remnants or may be converted to LDL and then catabolized. Consistent with the decreased triglyceride transport in FH, VLDL apoB secretion is thus reduced, and its remnants are largely converted to LDL rather than cleared from plasma. Furthermore, a major portion of apoB is also secreted as IDL/LDL. Accordingly, mean LDL apoB transport is significantly higher in FH (23 mg/kg per day) than in normal and HTG subjects (16 and 18 mg/kg per day, respectively).

Several reports describe the transient induction of HTG by high-carbohydrate diets in normal, diabetic, and HTG subjects. In those studies a [3H]glycerol triglyceride tracer and radioiodinated VLDL were used to demonstrate that increased VLDL triglyceride secretion on the high-carbohydrate diet was accompanied by increased VLDL apoB remnant catabolism in normal and HTG subjects. Because of the increased triglyceride transport and VLDL remnant catabolism, LDL apoB concentration fell. We confirmed these findings in normal subjects. In contrast, no loss of VLDL remnants occurred in FH subjects during a similar carbohydrate-induced HTG. Rather, all apoB was still channeled to LDL, which remained the site of apoB catabolism in these FH subjects. These findings emphasize the singular importance of apoB as a transport protein for cholesterol esters in FH. They also raise questions about the purpose and control of this metabolic fork by which the catabolism of VLDL apoB remnants is prominent in HTG individuals, less prominent in normal subjects, and greatly reduced in FH subjects. We speculate that control is exerted at this fork, by which the excess apoB required for triglyceride secretion but not cholesterol ester transport is removed from plasma by the hepatic uptake of VLDL remnants. Thus, LDL apoB production depends on the sum of apoB derived from VLDL and that secreted as IDL/LDL particles, the latter pathway being prominent in metabolic states in which hepatic cholesterol esters are increased. The metabolic
reactions by which VLDL remnants are catabolized are a subject of intense study in many laboratories, but a critique of this subject is beyond the scope of this review; however, apoE, the C apolipoproteins, and lipoprotein lipase are almost assuredly involved.

ApoB secreted as intermediate-sized particles is primarily a carrier for cholesterol esters, a role it shares with apoB remnants derived from the VLDL delipidation pathway. These two populations of apoB particles are channeled into LDL, and it appears likely that they retain, in part, their metabolic individuality and thus contribute to the physical heterogeneity of LDL.\(^ {17}\)

Examination of the LDL apoB production rate and residence time (the reciprocal of the FCR) as determinants of LDL apoB concentration further clarifies the process by which apoB may be catabolized as VLDL remnants or channeled through IDL to LDL. In normal, FH, and HTG subjects, LDL apoB mass, or concentration, correlates significantly with LDL apoB production \((r = .55, P < .01; \text{Fig 3A})\). However, LDL apoB mass in normal and HTG subjects is independent of total apoB secretion. This distinction between total apoB secretion and LDL apoB transport results from the loss from plasma of VLDL remnants in normal and HTG subjects that occur independently of LDL concentration. LDL apoB mass also correlates with LDL apoB residence time \((r = .54, P < .01; \text{Fig 3B})\). Thus, both LDL apoB production and LDL apoB residence time appear to determine LDL apoB mass in a manner independent of VLDL apoB metabolism. When plotted against each other, however, these kinetic determinants of LDL apoB concentration are not significantly correlated \((r = - .33, P > .1)\), implying that the regulation of LDL production and LDL catabolism is not tightly coordinated.

The FCR of LDL in FH

The FCR of LDL is decreased in FH.\(^ \text{3} \) To understand this phenomenon we need to appreciate evolving concepts of hepatic cholesterol metabolism. Hepatic free cholesterol in humans turns over rapidly, with a \(T_{1/2}\) of 72 minutes.\(^ {43} \) A portion of this cholesterol is considered to belong to a metabolically active pool of free cholesterol that exists in dynamic equilibrium with cholesterol esters through the action of the enzymes acyl coenzyme-A:cholesteryl acyl transferase (ACAT) and a cholesteryl ester hydrolase.\(^ {44,45} \) Rates of bile acid production,
cholesterol synthesis, and LDL receptor expression are thought to be controlled by this putative free cholesterol pool. Wollett et al.46 Daumerie et al.47 and Wollett et al.48 have demonstrated the ability to modulate this control mechanism by altering hepatic uptake of saturated and unsaturated fatty acids. When the intrahepatic free cholesterol concentration increases, through the action of ACAT the cholesterol ester pool enlarges, and production of cholesterol ester–enriched lipoproteins increases.49

This concept of a hepatic regulatory free cholesterol pool that exists in rapid equilibrium with a cholesterol ester pool rationalizes the postulate that LDL receptor expression is normally decreased in patients with heterozygous FH, who appear to have an increase in hepatic total cholesterol and especially cholesterol ester content. At the maximal level of transcription, the single normal allele in FH heterozygotes generates about 50% of the normal complement of expressed LDL receptors.60 However, transcription of this single allele would be suppressed in the presence of an increased hepatic cholesterol level, just as would be the case in the normal hepatocyte. Because there is only a single normal allele in FH heterozygotes, the amount of gene product is reduced to about half that of a normal cell having the normal allele in FH heterozygotes, the amount of gene product is reduced to about half that of a normal cell having the normal complement.

To examine the relation between the FCR of LDL and hepatic cholesterol synthesis, we used two perturbations known to suppress cholesterol synthesis, the drug lovastatin and a high-carbohydrate, low-fat diet.20 Both of which cause inhibition of HMG-CoA reductase.51–54 Seven FH patients were studied under basal conditions while receiving a standard diet and were then restudied either after restabilization on the high-carbohydrate diet (3 subjects) or while receiving 40 mg lovastatin daily (4 subjects). The details of the diet study have been reported.20 Lovastatin decreased LDL cholesterol concentration by 46% and LDL apoB mass by 49%, while carbohydrate feeding lowered LDL cholesterol by 34% and apoB mass by 41%. Fig 4 summarizes our observations on the FCR of LDL apoB in normal and FH subjects.17–20

The interesting finding is that the decreased FCR in FH subjects was normalized by either of these two hepatic cholesterol–reducing perturbations.

The data on the change in LDL kinetics resulting from these two perturbations are combined in the Table; the change in the rate of plasma clearance of LDL is tabulated as change in residence time, which is the reciprocal of the FCR. Although both interventions produce a decrease in LDL apoB mass, there is no consistent change in LDL apoB transport (or production). In contrast, the residence time of LDL apoB is uniformly decreased, and this change, reflecting an increase in the rate of LDL catabolism, was the primary determinant accounting for the fall in LDL apoB mass. The decrease in residence time of LDL with lovastatin is consistent with the initial report on the effect of this drug on apoB metabolism in FH.55

The normalization of the FCR of LDL by lovastatin or a high-carbohydrate, low-fat diet is in agreement with reports that bile acid sequestrants, which increase hepatic cholesterol catabolism, also decrease LDL concentration in FH heterozygotes by increasing apoB receptor–mediated LDL uptake by the liver.56–59 Thus, as shown by these three perturbations, under standard conditions the catabolic rate of LDL in heterozygous FH is suppressed below an upper limit permitted by the genetically determined receptor defect, and the resultant increase in plasma LDL concentration can be reversed by these interventions that deplete hepatic cholesterol.

Relevant to the relation of hepatic cholesterol ester content to apoB metabolism is a report of an FH kindred in whom individuals with defective LDL receptors have either normal or elevated plasma LDL concentrations.60 The heterozygous FH individuals with both normal or high LDL apoB levels had similar decreases in the FCR of LDL. However, those patients with high LDL apoB concentrations also had increased LDL apoB production, so it would appear that the difference in plasma LDL concentration was caused by the difference in the production rates. We speculate that those subjects with high production rates have a greater increase in their hepatic cholesterol ester pool and that their plasma LDL would be more responsive to the LDL-lowering effects of dietary carbohydrate or pharmacological depletion of hepatic cholesterol.

The composite data presented here on apoB secretion and LDL production and residence time are consistent with the premise that a hepatic cholesterol overload is the primary determinant of apoB metabolism in FH heterozygotes. The response of the liver appears similar to that seen during dietary cholesterol feeding, in which the hepatic uptake of cholesterol-laden chylomicron remnants cannot be suppressed.61 On a high-cholesterol diet, hepatic cholesterol synthesis and apoB receptor expression are reduced, and both cholesterol esterification and the production of cholesterol ester–enriched apoB-containing lipoproteins increases.44,45,67

In contrast to rodents, in humans the liver is not thought to be a major site of cholesterol synthesis, which occurs primarily in peripheral tissues,62 but in the WHHL rabbit sterol synthesis is not increased in these peripheral sites.7 Similarly, cholesterol kinetic turnover...
studies in hypercholesterolemic patients show no increase in cholesterol synthesis in the slow turnover of pools that reflects peripheral tissue sterol metabolism. Normally, LDL clearance occurs primarily by the hepatic apoB/E receptor pathway. In the WHHL rabbit, because of the absence of the apoB receptor and the increased production of LDL, plasma LDL concentration rises, and this rise causes an increase in nonreceptor-mediated LDL cholesterol uptake. However, cholesterol balance in extrahepatic tissues remains nearly normal, as demonstrated by minimal changes in the cholesterol ester content of most of these tissues. In contrast, hepatic cholesterol ester content in the WHHL rabbit is increased, as it is to a lesser extent in the lung and kidney.

By what mechanism could a hepatic cholesterol overload occur in FH heterozygotes? While some homozygous FH patients apparently have a positive sterol balance, most investigators find normal rates of cholesterol production in heterozygous FH subjects. Decreased cholesterol synthesis, however, is reported in the WHHL rabbit. In circulating mononuclear cells recovered from human FH heterozygotes, HMG-CoA reductase activity and mass are both reduced and are further decreased in homozygotes. This finding is consistent with reports that monocytes maintained in culture in a hypercholesterolemic environment also increase their cellular cholesterol and cholesterol ester content. In macrophages, however, the scavenger receptor provides the likely mechanism by which cholesterol esters accumulate, but it is not found in hepatocytes.

Decreased bile acid production is generally found in heterozygous FH. Cholesterol 7α-hydroxylase, the control enzyme for bile acid synthesis, is induced or suppressed, respectively, by the supply of cholesterol or bile acids to the liver. Thus, decreased bile acid production appears inconsistent with an increase in hepatic cholesterol in FH, though it could be the cause of such an increase. However, most investigations of bile acid metabolism have been conducted in the rat. In humans, bile acid production appears to be regulated by a hepatic cholesterol pool derived from either newly synthesized or plasma-derived cholesterol; Mitchell et al. link bile acid synthesis to cholesterol synthesis by demonstrating a reduction in bile acid production in response to inhibition of cholesterol synthesis with lovastatin. In apparent contrast to the rat, a primate model, the African green monkey, demonstrates a reduction in activity and hepatic mRNA abundance of cholesterol 7α-hydroxylase on dietary cholesterol loading, conditions under which suppression of hepatic cholesterol synthesis also occurs. From this primate model it can be postulated that an increase in the putative hepatic cholesterol regulatory pool in FH is associated not only with suppression of HMG-CoA but also with inhibition of bile acid production.

Two processes appear to predominate in the hepatic control of the metabolism of plasma apoB-containing lipoproteins. One involves cholesterol balance across the liver and the other involves bile acid production. Although the latter is decreased in FH, the cause remains unclear; however, it appears likely that the putative cholesterol regulatory pool is the site toward which we must look in attempting to understand the altered hepatic cholesterol physiology in FH. Whether the reduction in bile acid production is a cause or a consequence of increased hepatic cholesterol is unknown. If the latter, then it is possible that the flux of tissue cholesterol through plasma to the liver is increased without a net change in total body cholesterol balance but with an increase in the hepatic steady-state cholesterol content. If so, one would anticipate an increase in LDL production together with a decreased LDL uptake by the liver, with a resultant rise in LDL concentration, as seen in these patients.

Plasma cholesterol esters are believed to be returned to the liver primarily by endocytosis of LDL, and the cholesterol ester transfer protein (CETP)-mediated transport of cholesterol esters from high-density lipoprotein (HDL) to VLDL/LDL in exchange for triglyceride is critical to this process. Plasma CETP activity has been measured in FH by several groups of investigators, and depending on the method of assay it is reported to be either increased or decreased.
Because of decreased VLDL secretion in FH (Fig 1), availability of VLDL triglyceride may be rate limiting for the transfer of HDL cholesterol esters. In fact, in normal subjects the availability of triglyceride becomes rate limiting for cholesterol ester transfer, and the increased transfer in HTG is largely due to the increased availability of VLDL triglyceride. Accordingly, one might anticipate that a low plasma triglyceride concentration in FH should correlate with a high HDL cholesterol level. In 49 of our patients with an isolated hypercholesterolemia and clinical criteria compatible with FH, HDL cholesterol and plasma triglycerides were negatively correlated \( (r = -0.35, P < 0.02) \). If VLDL triglyceride is rate limiting for HDL cholesterol ester transfer, a perturbation that increases VLDL triglyceride availability in FH should cause a fall in HDL cholesterol. Plasma lipids were measured in a subset of 5 FH subjects on a control diet consisting of 45% carbohydrate, 40% fat, and 15% protein, followed by a diet consisting of 90% carbohydrate and 1% fat (Table 1 in Reference 20). On the high-carbohydrate diet, which increased VLDL triglyceride production, plasma triglycerides rose an average of 110 mg/dL (SD, 51) and HDL cholesterol decreased an average of 15 mg/dL (SD, 4.3) \( (P < 0.05) \). These data are consistent with the hypothesis that reduced VLDL triglyceride availability in FH may be rate limiting for cholesterol ester transfer. If so, how much of the cholesterol ester found in LDL is derived from the action of hepatic ACAT? This pathway appears to occur in cholesterol ester transfer deficiency, in which apoB-containing lipoproteins are reported to contain ACAT-derived cholesterol esters, presumably of hepatic origin. LDL cholesterol ester levels are high in FH partly because of impaired apoB transport through the apoB receptor pathway. If net transfer of cholesterol esters from HDL to apoB lipoproteins is also limited in FH, then an alternate route for the return of plasma cholesterol esters to the liver must be sought. Measurement of reverse cholesterol transport in humans shows a major flux of free cholesterol from HDL to the liver. Conversely, in humans the transfer of cholesterol esters from HDL directly to hepatocytes is believed to be of low capacity compared with the LDL pathway. Yet such a pathway for the selective uptake of cholesterol esters from HDL may be apoE mediated, and plasma apoE levels are increased in FH. Kinetic studies have also quantified the physiological importance of such a pathway in rabbits. Thus, mechanisms exist for hepatic uptake of HDL-associated free cholesterol or cholesterol esters, but whether they are sufficient to account for the increased hepatic cholesterol in FH patients is unknown.

Finally, we propose an alternate and quite speculative hypothesis that could explain at least some of the metabolic features of heterozygous FH that cannot be understood within the framework of the classic LDL receptor paradigm. An interesting concept has evolved from the study of patients heterozygous for thyroid hormone resistance, in whom a mutated and nonfunctional thyroid receptor protein may bind inappropriately to the DNA regulatory element and suppress transcription of the otherwise normal remaining receptor gene. The transcription of the LDL receptor is now known to be controlled by a steroid regulatory element (SRE) that is activated by SRE-binding proteins (SREBP). A decrease in cellular cholesterol activates transcription of the gene through an increased binding of these proteins to the SRE. While the LDL receptor is not known to be a DNA-binding protein, it might participate in the regulation of the SREBP, perhaps at an extranuclear level. Drawing on the thyroid hormone receptor analogy, it is conceivable that a mutated LDL receptor protein may exist and under basal conditions may block SREBP activation of the regulatory element for the normal gene, thus giving rise to the reduced number of LDL receptors. However, when hepatic cholesterol is depleted by diet or drugs, an increased stimulus is provided for the binding of SREBP to the SRE, which overcomes the suppressive action of the mutated receptors. The resultant increased transcription of the normal gene would then provide the added receptors required to normalize the FCR of LDL.

In summary, tracer kinetic data support the hypothesis that apoB is metabolized in FH in a manner compatible with an increase in hepatic cholesterol esters. Thus, the reduced VLDL secretion in FH subjects is predictable and consistent with a triglyceride transport that is reduced compared with that in normal or HTG individuals.

Decreased catabolism of VLDL and its remnants is a consistent finding in FH subjects. The metabolic fork, by which VLDL remnants are either targeted for catabolism or converted to LDL, appears to be the site of a fundamental difference in apoB metabolism between FH and normal or HTG individuals. The control exercised over these diverging pathways emphasizes the coordination of the roles of apoB as a transporter of triglycerides and cholesterol esters. In FH the channeling of secreted VLDL apoB into LDL, plus the additional secretion of smaller IDL/LDL particles, accounts for the increased production of LDL apoB found in these patients.

The hypercholesterolemia of the FH heterozygote is a consequence of both an increased production of LDL apoB and a reduction of cellular LDL receptors. The resultant decrease in the FCR of LDL apparently occurs in response to an increase in the hepatic cholesterol ester pool and is reversible, since it may be normalized by depleting hepatic cholesterol. The altered metabolism of apoB in FH is understandable when viewed as a response by a liver overloaded with cholesterol.

It must be remembered, however, that this analysis is based on plasma lipoprotein kinetic measurements in humans that have been interpreted in terms of data obtained from physiological studies of animal models of FH. The recently described strain of rhesus monkeys that exhibits a defective LDL receptor should be a useful animal model to further evaluate this hypothesis. In these animals, kinetic and analytic studies of plasma lipoproteins could be combined with an investigation of hepatic cholesterol metabolism and careful measurements of the cholesterol content of the liver. While it is tempting to speculate on a mechanism by which the mutated receptor protein may play a role in the development of the clinical syndrome of heterozygous FH, we are unaware of any current evidence that directly supports this thesis.
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W R Fisher, L A Zech and P W Stacpoole

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