Substrate Delivery as a Determinant of Hepatic ApoB Secretion

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Lipoprotein levels in plasma are a function of the rate at which they are produced as well as the rate at which they are catabolized. Both processes are critical. Yet the greatest proportion of clinical investigative energy by far has focused on the latter, with relatively little interest, by contrast, in the former. To be sure, considerable work has been done by basic scientists to elucidate the steps involved in the formation and secretion of a hepatic particle (for a general review, see Reference 1). However, for the most part, this knowledge has not yet altered our approach to the classification and therapy of dyslipoproteinemias in humans. This situation stands in marked contrast to the errors of catabolism, in which advances in basic knowledge have been tightly coupled to a better understanding of the pathogenesis of distinct clinical disorders. As a result, among physicians there is a widespread failure to appreciate that not only can hepatocytes vary the composition of the apolipoprotein (apo)B particles that they secrete but even more importantly, that they can also vary the rate at which such particles emerge into the circulation. The purpose of this review is to demonstrate that such differences can be related in large degree to differences in the delivery of various substrates to the liver, and if this is recognized, how our understanding of the pathophysiology of a number of human dyslipoproteinemias can be increased.

Effect of Carbohydrate on the Assembly, Secretion, and Plasma Metabolism of VLDL

Perhaps because triglycerides are the major lipid component of very low density lipoprotein (VLDL), the general view appears to be that the rate of secretion of such particles is merely a single and direct function of the corresponding rate of triglyceride synthesis within the hepatocyte. Experimentally, however, this does not appear to be the case. For example, increasing the glucose concentration in the medium surrounding HepG2 cells results in increased intracellular triglyceride synthesis and secretion but does not alter the rate of apoB secretion.2 The effect of glucose under these circumstances, therefore, is to alter the composition of the secreted apoB particles so that they contain more triglyceride and are larger and more buoyant in consequence. These in vitro findings closely mimic those previously observed in humans. Abbott et al3 examined the effect of a high-carbohydrate, low-fat diet on VLDL triglyceride and apoB metabolism in Pima Indians, some of whom were diabetic and others of whom were not. In both groups, they showed that hepatic triglyceride secretion was increased on the high-carbohydrate diet, whereas apoB output was unchanged. Exactly the same pattern was observed by Melish et al4 who confirmed the dissociation in triglyceride and apoB secretion rates that resulted from introduction of a high-carbohydrate diet. These findings have been considerably extended by the kinetic studies of Fisher et al5 and Staapoole et al.6 Using deuterated leucine, they determined that the liver secreted two types of VLDL particles that differed in composition and metabolic fate. One pathway was characterized by the secretion of large triglyceride-enriched particles, some of which were metabolized along a delipidation pathway to low density lipoprotein (LDL), while the other pathway featured the secretion of much smaller particles, most of which were rapidly converted to LDL via intermediate density lipoprotein (IDL). Carbohydrate feeding altered the pattern of hepatic apoB secretion so that a higher proportion of the particles than before were triglyceride enriched.6 It should be noted that these investigators, as have almost all others for the past two decades (for a general review, see Reference 7), were forced to adopt a multicompartmental model with multiple inputs and outputs to describe the plasma metabolism of the apoB100 triglyceride-rich lipoproteins; one characteristic of most such models being that the liver secretes different forms of hepatic apoB lipoproteins into the circulation.

The metabolic fate of larger VLDL particles had some time ago been shown by Packard and coworkers to differ from the smaller ones in that more of the former compared with the latter are directly catabolized without being converted to LDL. Ginsberg et al7 also demonstrated that carbohydrate feeding in mildly hypertriglyceridemic patients predictably altered these proportions. That is, the proportion of VLDL apoB catabolized without reaching LDL was significantly greater on the high-carbohydrate compared with the basal diet, resulting in lower LDL levels than would otherwise be the case.

Taken together, these in vitro and in vivo data indicate that hypertriglyceridemia due to increased delivery of carbohydrate to the liver is characterized by the secretion of a greater proportion than normal of
apoB100 particles that are particularly enriched in triglyceride. However, because the rate of apoB secretion remains normal and because, in contrast to normals,10 the conversion rate of VLDL to LDL in such patients is reduced, the number of LDL particles will be normal, not elevated. Moreover, hypertriglyceridemia will lead to increased cholesterol ester–triglyceride shifts mediated by cholesterol ester transfer protein (CETP), a phenomenon that is almost certainly responsible for the increased triglyceride content of all of the lipoprotein classes that have been reported in such patients.11 Of possible importance, though, these re-modeled LDL particles may be more atherogenic than they were in their native state, since they usually end up being smaller and denser than normal.

The intracellular consequences of increased delivery of carbohydrate are known only in outline. The activities of fatty acid synthetase, glucose-6-phosphate dehydrogenase, and malic enzyme12-14 all increase, resulting in elevated triglyceride synthesis. Cholesterol ester synthesis does not increase, perhaps because, compared with lactate or fatty acids, glucose appears to be a poor substrate for cholesterol synthesis.15 Indeed, there is evidence in rats that increased glucose feeding results in reduced 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase activity and reduced cholesterol synthesis.16,17 As we discuss below, these effects may explain the difference in apoB response elicited by increased delivery of exogenous fatty acids compared with that observed with increased glucose delivery.

Effect of Increased Lipid Delivery on the Assembly, Secretion, and Plasma Metabolism of VLDL

Increased Delivery of Fatty Acids

Our concepts are to an important degree a function of the experimental models we choose, all of which, to larger or lesser degree, differ from the intact liver in the intact human. Many investigators, however, have chosen to study HepG2 cells, and this provides a body of work on which the same model has been used. In that regard, a number of laboratories have now shown that increased delivery of fatty acids to HepG2 cells significantly increases the rate at which apoB particles are secreted.18-20 Because no change in apoB mRNA has been observed, it has been concluded that such regulation must be cotranslational or posttranslational. Indeed, Dixon et al21 have presented evidence to support this view. They have shown that substantially more apoB molecules are synthesized in the rough endoplasmic reticulum than are finally secreted from the cell. They also observed that oleate changes this proportion by decreasing the number of molecules degraded and increasing the number secreted. However, in contrast to glucose, the apoB particles secreted by HepG2 cells in response to fatty acids are not markedly enriched in triglyceride.2 To be sure, the mass of triglyceride that is synthesized and exported from the hepatocyte rises in both instances. In the case of glucose, this is achieved by increasing the triglyceride mass per particle. By contrast, in the case of fatty acids, the mass of triglyceride per particle increases only marginally, whereas the number of particles secreted per unit time rises substantially. Therefore, one would anticipate increased fatty acid delivery to the liver to result in increased secretion of VLDL particles in vivo. Not only has the number of precursor particles increased, but also, because these VLDL particles are normal in composition, they are more likely than the triglyceride-enriched large VLDL particle characteristic of glucose-induced hypertriglyceridemia to be converted to LDL. For both of these reasons, therefore, increased delivery of fatty acids to the liver will result in increased numbers of LDL particles. The combination of VLDL of normal composition with increased LDL particle number has been documented in a group of hypertriglyceridemic patients and contrasts with the findings already noted of triglyceride-enriched VLDL with normal LDL particle number in others who also had type IV hyperlipoproteinemia.22

Because LDL particle number is a major determinant of atherogenic risk (see reviews in References 23-25), the clinical risk of the two forms of hypertriglyceridemia described above is markedly different and so also are the potential approaches to therapy. Moreover, the correspondence between these pathophysiological data and the already documented in different genetic types of hypertriglyceridemia should not be overlooked. Thus, familial hypertriglyceridemia is characterized by triglyceride-enriched VLDL particles, normal apoB secretion rates, normal LDL particle number, and no noticeable increase in cardiovascular risk.26,27 By contrast, the hypertriglyceridemic variant of familial combined hyperlipidemia or hyperapoB is characterized by VLDL of normal composition, an increased secretion rate of hepatic apoB lipoproteins, increased LDL particle number, and increased risk of premature coronary artery disease.26,28-30

The processes that regulate whether a newly synthesized apoB molecule proceeds to be incorporated into a lipoprotein particle or whether it is degraded without being secreted are under active study. Work from our laboratory has indicated that the rate of cholesterol ester synthesis in the rough endoplasmic reticulum may be important in this regard. Thus, when fatty acid delivery to HepG2 cells increases, cholesterol ester synthesis increases in parallel with triglyceride synthesis, albeit at a much less absolute rate.20 If the rate of cholesterol ester synthesis is reduced by either an HMG CoA reductase inhibitor or an acyl coenzyme A cholesterol acyltransferase (ACAT) inhibitor, the rate of apoB secretion is reduced as well.31 By contrast, exogenous glucose increases the rate of triglyceride synthesis but does not increase the concomitant rate of cholesterol ester synthesis.2 In this instance as well, the rate of apoB secretion follows that of cholesterol ester, not triglyceride synthesis.

Increased delivery of fatty acids appears to result in an increase in HMG CoA reductase activity,1 an effect that would increase cholesterol synthesis and, as noted above, contrasts with the reduction in HMG CoA reductase activity induced by glucose.16,17 The recent finding that oleate-stimulated secretion requires an apoB of critical length is consistent with posttranslational control but obviously does not directly establish a role for ACAT in determining whether an apoB molecule escapes presecretory degradation.21

Much work remains to be done, and not all results are in accord with the model we have discussed. For example, in contrast to our results, Arrol and coworkers22 found apoB secretion to rise with glucose challenge to HepG2 cells; the experimental design and methods,
however, differed considerably from ours. The recent report by Wetteran et al. that a microsomal triglyceride transfer protein is absent in four patients with abetalipoproteinemia is also of considerable interest. That such a protein might be essential to effect movement of core lipid through the membrane bilayer into the interior of the apoB molecule as it coils into its final conformation may well be the case. This particular protein, however, is apparently nonspecific with regard to lipid transfer, and so these observations would not discriminate as to whether it is triglyceride, cholesterol ester, or both that rescue the apoB molecule from hydrolysis. On the other hand, in support of our hypothesis, the ACAT inhibitor CI-976 has been shown to lower plasma cholesterol and apoB in rabbits fed a cholesterol-free diet, to reduce apoB secretion from monkey livers perfused with this agent, and to lower plasma triglyceride and apoB levels in both cholesterol- and sucrose-fed rats.

Role of Cholesterol in Regulation of Hepatic ApoB Secretion

Heimberg and his colleagues (Khan et al.) in a series of studies have shown cholesterol to be a critical requirement for the secretion of VLDL. Khan et al., for example, demonstrated that lovastatin reduced hepatic VLDL secretion and that this change was directly proportional to a decrease in cholesterol and cholesterol ester synthesis, whereas it was not related to the rate of triglyceride synthesis. Moreover, the rate of VLDL secretion returned toward normal when cholesterol or LDL was added to the medium perfusing the rat livers, observations that were supported by those obtained later in intact animals. Their work, however, has been done in the presence of fatty acids, and data obtained from HepG2 cells indicate that influx of cholesterol itself into the cell causes apoB secretion to rise. The most detailed examination of this phenomenon to date has been done by Dashti. In brief, she demonstrated that when either 25-hydroxycholesterol or LDL was added to the medium, apoB secretion was increased from HepG2 cells and that such changes paralleled the mass of cellular cholesterol ester but not triglyceride. Moreover, the cholesterol content of the secreted apoB particles mirrored these changes, increasing as apoB secretion increased. With 25-hydroxycholesterol, only a modest increase in apoB mRNA content was documented (55%) in the face of a several-fold increase in apoB secretion, whereas with LDL, no change in mRNA was observed. These results, as in the case of fatty acids, are most consistent with posttranslational modification being the major stage that regulates apoB secretion.

Another observation in that study was also of considerable interest, namely that the LDL receptor activity of HepG2 cells was only modestly reduced when either 25-hydroxycholesterol or LDL was added to the medium. This contrasts markedly, of course, with the response observed in fibroblasts, in which LDL receptor activity in normal cells is almost completely downregulated when LDL is added to the medium. Havekes and his colleagues have previously commented on these differences, which they attributed to subcellular compartmentalization of cholesterol, with a relatively small pool being critical for regulation of LDL receptor activity. That such compartmentalization exists seems almost certain. Exogenous cholesterol must first pass through the lysosome and then, by processes still not well defined, reach the critical intracellular sites before it or its metabolic products can affect synthesis of cholesterol and receptors.

The sequence that follows entry of an LDL particle into a fibroblast is much more straightforward than in the hepatocyte. All of the cholesterol molecules that enter a fibroblast will be distributed within the membranes of the subcellular organelles and in consequence, cause downregulation of both cholesterol and LDL receptor synthesis. The more cholesterol that enters the cell, the more these two processes will be affected. However, the hepatocyte can secrete apoB100 particles, and as just noted, in response to increased uptake of cholesterol the rate of secretion of these particles will rise. Moreover, there is evidence that lipid can be added to apoB particles that have left the endoplasmic reticulum and are in transit through the Golgi. The increased content of cholesterol in the apoB particles secreted from HepG2 cells under these circumstances may reflect transfer of cholesterol from the lysosome to the Golgi and then directly out of the cell. The failure of the complete downregulation of LDL receptors in the hepatocyte after exposure to LDL might then relate to these two phenomena: an increased secretion rate of apoB particles and resorption of important amounts of cholesterol that had just entered the cell through the LDL uptake pathway. Both would act in concert to shunt cholesterol from the cell and so reduce the tendency to decreased LDL receptor and cholesterol synthesis. We will return to these concepts in the discussion of apoB kinetics in patients with the nephrotic syndrome and familial hypercholesterolemia. On the other hand, there are clearly other mechanisms that also act within the hepatocyte to regulate LDL receptor activity, and as the studies of Davis and colleagues (Dueland et al.) indicate, 7α-hydroxylase activity may certainly play a key role in this regard.

Physiological Consequences of Increased Lipid Delivery to the Liver

There are now a series of studies, both in vitro and in vivo, demonstrating that hepatocytes can modify the rate and type of apoB particle secreted in response to uptake of chylomicron remnants or β-VLDL. Among the most interesting are a pair of studies by Craig et al., who compared the effects of chylomicron remnants and β-VLDL on lipid and apoprotein secretion by HepG2 cells. In brief, they showed that uptake of both types of particles increased apoB secretion but that chylomicron remnants, which are rich in triglyceride, resulted in the secretion of more buoyant, triglyceride-rich apoB particles, whereas VLDL remnants that are rich in cholesterol produced denser, cholesterol-rich apoB particles. In both instances, the increase in apoB secretion paralleled the changes in intracellular cholesterol ester content more closely than differences in triglyceride. However, when triglycerides were the major lipid entering the cell, they were also the principal component in the apoB particles leaving it. When cholesterol was the major lipid entering the cell, secretion of an apoB particle with a greater cholesterol content was the result.
Beyond this, it has been shown that dietary content and prefeeding will alter hepatic apoB metabolism. Fungwe et al. demonstrated that an increase in dietary cholesterol resulted in progressive increases in VLDL secretion of particles that contained increasing amounts of cholesterol ester. Hepatic triglyceride synthesis increased in hand in hand with increased dietary cholesterol, suggesting important linkages between the two. These investigators concluded that both cholesterol and fatty acids can increase the rate of hepatic apoB secretion but that the specific composition of the particle, i.e., the relative proportion of cholesterol or triglyceride, depended on whether cholesterol or fatty acid was the preponderant metabolic stimulant. A recent provocative observation demonstrating a conditioning effect of diet on hepatic lipid secretion was made by Quarfordt and colleagues when they observed that infusion of chylomicrons into cholester-fed rats resulted in sudden substantial increases in plasma cholesterol levels. The cholester appeared to be of hepatic origin, and the increase in plasma levels represented short-term recruitment into the plasma from liver stores. No such changes were seen in chow-fed rats. Finally, Van Heek and Zilversmit have shown that cholester-fed rabbits have increased VLDL production when fed coconut oil but not when fed olive oil.

All of this must be added to the existing evidence that VLDL secretion increases in the postprandial state in animals and humans. Perfused liver studies in both pigs and rats have shown that the liver in the postprandial state secretes more VLDL apoB than in the fasting state. In humans, Cohn et al. observed that apoB100 levels in the d > 1.006 g/mL supernate increase significantly after a fat-rich meal, suggesting that hepatic lipoproteins contribute to postprandial hypertriglyceridemia. Genest et al. had also previously observed a similar small but significant increase in VLDL apoB100 levels in normal subjects after an oral fat load. These observations were significantly extended by Cohn et al. when they determined the effects of fasting and feeding in humans on production rates of VLDL and LDL apoB100 by using deuterated leucine. They showed that in the fasting state LDL apoB100 production exceeded that of VLDL apoB100, whereas these relations were reversed in the postprandial state. Taken together, therefore, considerable evidence has now been amassed that the liver can vary the type and quantity of apoB particles secreted and that these differences can largely be related to the load and type of lipid it has received.

Pathological Syndromes With Increased Delivery of Lipid to the Liver

HyperapoB refers to that group of dyslipoproteinemias in which the cardinal feature is overproduction of hepatic apoB lipoproteins. In all cases to date, the overproduction can be related to increased delivery of either fatty acids, sterol, or both to the liver.

Increased Delivery of Fatty Acid

In some cases, the primary metabolic fault responsible for an increased production rate of hepatic apoB particles is a reduced maximal rate of fatty acid uptake in key peripheral sites such as adipose tissue. In such patients, chylomicron triglyceride clearance is decreased, and the maximal rate of triglyceride synthesis in their adipocytes is reduced. Acylation stimulating protein appears to be the most potent stimulant of intracellular triglyceride synthesis yet described, and skin fibroblasts cultured from patients with hyperapoB have shown significantly less triglyceride synthesis in response to acylation stimulating protein associated with a reduced cell surface association for this protein. These observations have now been confirmed and extended by Kwiterovich and coworkers.

On the other hand, Brunzell and colleagues have noted another abnormality, heterozygous lipoprotein lipase deficiency, in patients with the same lipoprotein phenotype that we have studied. The pathogenesis of the dyslipoproteinemia in both instances might be as follows. After an oral fat load, fewer fatty acids than normal are deposited in adipose tissue. The reduced rate of triglyceride synthesis in adipocytes results in a decreased rate of hydrolysis of chylomicron triglycerides due to free fatty acid product inhibition of lipoprotein lipase activity. By default, delivery of fatty acids to the liver increases in the form of either free fatty acid or chylomicron remnants with a higher triglyceride content than normal. This increased delivery of fatty acids to the liver results, in turn, by the mechanisms outlined above, in increased hepatic apoB lipoproteins. A very different and very interesting mechanism has been suggested by Williams and coworkers. Their in vitro work suggests that lipoprotein lipase-mediated reuptake of newly secreted apoB particles occurs to an important degree. Reduction in lipoprotein lipase might then lead to decreased reuptake, which then results in increased release of apoB particles into the circulation. More work is required to determine more precisely the association between lipoprotein lipase deficiency and plasma apoB levels and, if it is confirmed, the mechanisms responsible.

Unfortunately, the system of lipoprotein phenotyping now in widespread use classifies dyslipidemias on the basis of lipid and lipoprotein lipid levels only and does not take into account the notion that the liver may vary the composition and quantity of apoB particles that it secretes. Accordingly, distinctions that are important with regard to pathogenesis and therapy are ignored. In any individual, type IV hyperlipoproteinemia, for example, could represent hypertriglyceridemia due to secretion of a normal number of triglyceride-enriched VLDL particles and a normal number of LDL particles or alternatively, it might be due to secretion of an increased number of VLDL particles of normal composition that in turn produce an increased number of LDL particles. It is the latter type, hypertriglyceridemia with an increased LDL particle number, that is particularly associated with increased risk of premature vascular disease. Given that reducing the number of LDL particles decreases the likelihood of progression of coronary lesions and increases the chance of significant regression of such lesions (for a review, see Reference 69), we believe that a lower apoB level should be the primary goal of therapy in such patients, not simply a reduction of plasma triglyceride and cholesterol levels.

Increased Delivery and/or Synthesis of Sterol to the Liver

There are a series of disorders that all share the features of either increased delivery of a sterol to the
liver or increased synthesis of sterol within the hepatocyte and that have all been reported to be associated with an elevated number of LDL particles in the plasma. They include betasitosterolemia,\textsuperscript{70} cholestasis,\textsuperscript{71} cholesterol ester storage disease,\textsuperscript{72} nephrotic syndrome, and familial hypercholesterolemia. In all, these changes are secondary and are a response to a primary fault lying elsewhere. The issue at hand, though, is to see how a critical fault at one site in sterol metabolism so unbalances the normal transport system that adjustments metabolically far removed must be made and that these adjustments result in overproduction of hepatic apoB lipoproteins.

Let us begin with betasitosterolemia. In this disorder, a plant sterol that is not normally absorbed can be detected in the plasma. Overall sterol absorption is increased in such patients,\textsuperscript{70} and increased delivery of dietary sterol to the liver may explain why many of these patients also have an elevated number of LDL particles.\textsuperscript{73} In support of this hypothesis is the marked reduction in LDL particle number that follows the use of bile acid sequestrants in such patients (Dr. H. Parsons, personal communication). To take another example, the intracellular mass of cholesterol ester increases in cholestasis, but delivery of regulatory cholesterol may be decreased because of sterol trapping within the lysosome. In consequence, cholesterol synthesis within the cell would be expected to be enhanced and apoB production to rise in turn. The best evidence that this sequence is indeed operative is found in the kinetic studies of Ginsberg and colleagues,\textsuperscript{72} who showed that apoB production was increased in such patients and was reduced after administration of lovastatin.

Increased clearance due to upregulation of hepatic LDL receptor activity has been widely believed to be the only important mechanism by which HMG CoA reductase inhibitors reduce plasma levels of LDL.\textsuperscript{74} However, there is now considerable evidence from in vitro studies\textsuperscript{20} from in vivo animal studies,\textsuperscript{38,75,76} and from human studies\textsuperscript{72,77-81} that a major if not the principal mode of action of such agents is to reduce the rate at which lipid-rich apoB particles are secreted from the liver. Moreover, the concordant results from such a wide variety of experimental data strongly supports, we believe, the model that we have suggested for regulation of apoB secretion.

Overproduction of hepatic apoB lipoproteins in the nephrotic syndrome is generally agreed to be one of its cardinal features.\textsuperscript{82,83} Cholesterol synthesis has been reported to be increased in experimental nephrotic syndrome,\textsuperscript{84-86} and if this also occurs in humans, it might of course be an important mechanism by which apoB production is increased. However, more appears to be at play. Some\textsuperscript{86} although not all\textsuperscript{87} investigators have noted a significant reduction in the removal rate of LDL from the plasma and have concluded that impaired catabolism is important in the pathogenesis of the dyslipoproteinemia. However, given that the liver is the major site for the removal of LDL from plasma and that the levels of LDL are markedly increased in such patients, the mass of sterol delivered each day to the liver would in fact far exceed normal. The striking feature, therefore, is not that the fractional removal rate of LDL is reduced somewhat in patients with the nephrotic syndrome but rather that LDL receptor synthesis is not completely suppressed, with fractional removal rates approaching those observed in homozygous familial hypercholesterolemia. The nephrotic syndrome would seem, therefore, to be an extreme and extremely paradoxical instance of the failure of the downregulation of LDL receptor synthesis in vivo.

However, the paradox becomes much less puzzling when the capacity of the liver to reexport a major portion of such cholesterol is taken into account. The evidence that VLDL particles can be larger in the Golgi than in the endoplasmic reticulum has been noted above.\textsuperscript{85,86} If cholesterol can move directly from the lysosome to the Golgi and then promptly leave the cell, it would never come into equilibrium with the critical sites within the cell at which LDL receptor synthesis is determined. As well, cholesterol that does penetrate the interior compartments of the cell more fully can stimulate increased apoB secretion, and so cholesterol export from the cell can also increase by virtue of this effect. The nephrotic syndrome would then be an in vivo example of the in vitro phenomenon already cited, namely failure of appropriate downregulation of LDL receptor activity in HepG2 cells exposed to LDL.

A similar explanation may apply to the issue of “independent” LDL production in patients with familial hypercholesterolemia. The evidence that increased delivery of cholesterol to the liver is associated with the production of increased numbers of denser-than-normal apoB particles with more cholesterol than normal has been cited above.\textsuperscript{41-49} Such particles also contain less triglycerides than normal and could, therefore, be rapidly converted to LDL. In the case of familial hypercholesterolemia, non-receptor-mediated removal of LDL from the plasma increases markedly, but if studies in the Watanabe rabbit apply to humans, then the total mass of sterol actually delivered to the liver per day is much above normal in such circumstances.\textsuperscript{88} Given that the capacity of the liver to catabolize cholesterol is so limited, the response noted just above occurs, namely an increased rate of secretion of apoB100 particles, some of which have more cholesterol in their core than others, and the latter are able to be converted much more quickly than the former to classical LDL.

The question as to whether independent secretion of LDL occurs in familial hypercholesterolemia has been debated on the basis of the analysis of kinetic data.\textsuperscript{89-92} Both factions agree that there is increased secretion of hepatic apoB lipoprotein particles that are denser than normal. Whether the particle that emerges from the liver initially has a density slightly less than 1.006 g/mL and is rapidly converted to LDL, or whether it first enters the plasma with a somewhat greater density and so immediately has the density characteristic of a classical LDL particle is an issue of real but probably limited significance. The more important point, certainly in the present context, is that both sides agree that a hepatic apoB particle quite different in metabolic behavior and composition from that usually encountered is characteristic of the disorder. That an increased number of apoB100 particles would be secreted in patients with familial hypercholesterolemia and that many should be enriched in cholesterol but relatively poor in triglyceride are features that would be anticipated from the analysis presented above.
Summary

The evidence that apoB particles secreted by the liver can differ in number and composition has been reviewed. No evidence has yet emerged that changes in apoB100 itself affect the rate of its secretion from the liver. The metabolic role of apoB appears to be the prevention of lipid accumulation within the liver cell: when delivery of lipid to the liver increases, apoB secretion will increase pari passu. This reality in no way detracts from the critical role played by the LDL receptor in determining the number of LDL particles in plasma, nor does it diminish the potential importance of intracellular processes such as \( \gamma \)-hydroxylase activity to also mediate LDL receptor activity. However, it should be obvious that variation in catabolism by itself cannot explain all that has been observed in physiological and pathological studies. On the contrary, the whole process must be taken into account—the rate at which apoB particles are added to the circulation, the rate at which they are converted to LDL, and the rate at which they are irreversibly removed from plasma—if we are to understand and appreciate this most peculiar and most important of transport systems.

References

to inhibition of both intestinal and liver ACAT. J Lipid Res 1993; 34:279-294


42. Brown MS, Faust JR, Goldstein JL: Role of the low density lipoprotein receptor in regulating the content of free and esterified cholesterol in human fibroblasts. J Clin Invest 1975;55:783-793

43. Havekes LM, DeWit ECM, Princen HMG: Cellular free cholesterol in HepG2 cells is only partially available for down-regulation of low-density lipoprotein receptor activity. Biochem J 1987;247:739-746


47. Dueland S, Trawick JD, Nenseter MS, MacPhee AA, Davis RA: Expression of 7α-hydroxylase in non-hepatic cells results in liver phenotypic resistance of the low density lipoprotein receptor to cholesterol repression. J Biol Chem 1992;267:22695-22698


75. Grundy SM, Veiga GL: Effects of lovastatin on very-low-density lipoprotein metabolism in subjects with combined hyperlipidemia: Evidence for reduced


84. Goldberg AC, Oliverina HCF, Quintae ELR, McNamara DJ: Increased hepatic cholesterol production due to liver hypertrophy in rat experimental nephrosis. *Biochim Biophys Acta* 1982;710:71-75


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doi: 10.1161/01.ATV.13.5.629
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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