Increased production of VLDL apoB-100 in subjects with familial hypercholesterolemia carrying the same null LDL receptor gene mutation

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Abstract **Early radiokinetic studies revealed that the classical metabolic defect in patients with familial hypercholesterolemia (FH) is hypocatabolism of LDL due to decreased LDL receptor activity. However, recent studies have suggested that hepatic oversecretion of apolipoprotein B-100 (apoB-100)-containing lipoproteins could also contribute to the markedly elevated plasma concentrations of LDL-cholesterol found in FH. The aim of this study was to examine the kinetics of apoB-100 labeled with a stable isotope (L-[5,5,5-D_3] leucine) in five normolipidemic controls and in seven well-characterized FH subjects that included six FH heterozygotes and one FH homozygote carrying the same null LDL receptor gene mutation. As compared with controls, the VLDL apoB-100 production rate was increased by 50% in the FH heterozygotes and by 109% in the FH homozygote. Furthermore, FH subjects had significantly higher LDL apoB-100 pool size and lower LDL apoB-100 fractional catabolic rate than controls. These results indicate that the elevation of plasma LDL-cholesterol found in FH is attributable to both decreased clearance of LDL and increased hepatic production of apoB-100-containing lipoproteins.**—Tremblay, A. J., B. Lamarche, I. L. Ruel, J-C. Hogue, J. Bergeron, C. Gagné, and P. Couture. **Increased production of VLDL apoB-100 in subjects with familial hypercholesterolemia carrying the same null LDL receptor gene mutation.** ***J. Lipid Res.*** **2004.** 45: **866–872.**

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Apolipoprotein B-100 (apoB-100) is a large glycoprotein of hepatic origin that plays an indispensable role in the assembly, secretion, and intravascular transport of distinct classes of lipoproteins. The role of the LDL receptor in the hepatic removal of apoB-containing lipoproteins is well established. ApoB-100 contains the domain required for interaction with the LDL receptor (1) responsible for approximately two-thirds of the clearance of apoB-containing lipoproteins (2). The importance of the LDL receptor in mediating hepatic uptake of apoB-containing lipoproteins is well illustrated in patients with heterozygous familial hypercholesterolemia (FH), in whom the presence of a mutant LDL receptor allele leads to a 2- to 3-fold increase of plasma levels of atherogenic apoB-containing lipoproteins and to premature coronary artery disease (3). Recently, a possible new role for the LDL receptor in the regulation of hepatic production of apoB-100 has been proposed on the basis of animal studies (4, 5). These studies suggest that the LDL receptor modulates the hepatic secretion of apoB-100 by promoting presecretory degradation of apoB-100 and by mediating the reuptake of newly secreted nascent apoB-100-containing lipoproteins, resulting in internalization and subsequent turnover of apoB-100. Therefore, the potential interaction between the LDL receptor and apoB-100 within the secretory pathway would impact upon hepatic apoB-100 secretion in a unique manner and would be expected to influence both clearance and secretion of newly synthesized apoB-100. However, the clinical relevance of this proposed new mechanism of regulation of hepatic apoB-100 production has not been established. In humans, the metabolism of apoB-100-containing lipoproteins has been investigated using various techniques that involved both FH homozygotes and heterozygotes carrying either receptor-negative or receptor-defective mutations. Consequently, it is not surprising that these studies have generated conflicting results, most probably related to differences in the methodology as well as genetic heterogeneity among subjects. In fact, most of the earlier radiokinetic studies revealed that the classical metabolic defect in FH patients is hypocatabolism of LDL due to decreased

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LDL receptor activity (6–9). In addition, recent kinetic studies using stable isotopes have suggested that hepatic oversecretion of apoB-100-containing lipoproteins would contribute significantly to the elevated plasma levels of LDL-cholesterol found in FH patients (10, 11), but these findings are not unanimous and remain controversial.

The aim of the present study was to clarify this issue by examining the kinetics of apoB-100 labeled with a stable isotope (L-[5,5,5-D_3] leucine) in five normolipidemic male controls and in a unique subgroup of seven well-characterized FH subjects that included six FH heterozygous males and one FH homozygous female carrying the same null LDL receptor gene mutation.

METHODS

Subjects

Six FH heterozygous males and five normolipidemic male control subjects matched for age and body mass index (BMI) with FH subjects were included in the study. All FH patients, including the homozygote, were carriers of the deletion >15 kb at the 5′ end of the gene (12) and were at least 16 years of age. The subjects included in this study had no known secondary hyperlipidemia. Subjects were excluded if they had acute liver disease, hepatic dysfunction, persistent elevations of serum transaminases, plasma triglyceride levels >4.5 mmol/l, a recent history of alcohol or drug abuse, diabetes mellitus, or a history of cancer. Furthermore, all participants had to be homozygous for the apoE3 allele and were unrelated at the first and second degree. All eligible FH patients had to withdraw lipid-lowering medications for at least 4 weeks before the kinetic study. The FH homozygote did not receive any LDL apheresis treatment for 4 weeks before the kinetic study. The research protocol was approved by the Laval University Medical Center ethical review committee, and written informed consent was obtained from each subject.

Experimental protocol for in vivo stable isotope kinetics

To determine the kinetics of VLDL, IDL, and LDL apoB-100, the subjects underwent a primed-constant infusion of L-[5,5,5-D_3] leucine while they were in a constantly fed state. Starting at 7 AM, the subjects received 30 identical small cookies every half hour for 15 h, each equivalent to 1/30th of their estimated daily food intake based on the Harris-Benedict equation (13), with 15% of calories as protein, 45% as carbohydrate, 40% as fat (7% saturated, 26% monounsaturated, 7% polyunsaturated), and 85 mg of cholesterol/1,000 kcal. At 10 AM, with two intravenous lines in place, one for the infusate and one for blood sampling, L-[5,5,5-D_3] leucine (10 μmol/kg body weight) was injected as a bolus intravenously and then by continuous infusion (10 μmol · kg body weight^{-1}/h) over a 12 h period. Blood samples (20 ml) were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h.

Characterization of plasma lipids and lipoproteins

Twelve hour fasting venous blood samples were drawn from an antecubital vein into Vacutainer tubes containing EDTA (0.1% final concentration) prior to the beginning of the kinetic study. Plasma was separated from blood cells by centrifugation at 3,000 rpm for 10 min at 4°C. Plasma cholesterol and triglyceride concentrations were determined with an Analyzer RA-1000 (Technicon Instruments Corporation, Tarrytown, NY), as previously described (14). The VLDL ($d < 1.006$ g/ml), IDL ($d = 1.006$–1.019 g/ml), and LDL ($d = 1.019$–1.063 g/ml) fractions were isolated from fresh plasma by sequential ultracentrifugation (15), and HDL-cholesterol was measured as previously described (16).

Quantification and isolation of apoB-100

ApoB concentrations in VLDL, IDL, and LDL were determined by noncompetitive ELISA using immunopurified polyclonal antibodies (Alerchek, Inc., Portland, ME) to calculate their respective pool sizes (PSs). The coefficient of variation for the apoB assay was between 6% and 10%, depending upon the region of the standard curve. ApoB-100 and apoB-48 were then separated by SDS polyacrylamide slab gel electrophoresis according to standardized procedures (17). Briefly, 50 μl of the VLDL, IDL, or LDL fractions was mixed with 50 μl of 3% SDS sample buffer and subjected to electrophoresis in 3–10% linear gradient polyacrylamide slab mini gels. Gels were stained overnight in 0.25% Coomassie Blue R-250 and destained for 7–8 h. Based on the assumption that both apoB-100 and apoB-48 have the same chromogenicity, the relative proportion of apoB-100 and apoB-48 was assessed by scanning each gel with laser densitometry (18). We scanned lipoprotein fractions from three different time points to calculate ratios and to estimate the average concentrations of apoB-100 using the total apoB concentration.

Isotopic enrichment determinations

ApoB-100 bands were excised from the polyacrylamide gels. The free amino acids were isolated from plasma by cation exchange chromatography. Plasma (0.3 ml) and the excised apoB-100 bands were hydrolyzed in 6N HCl at 110°C for 24 h (19). The amino acids were then converted to the *N*-propyl ester *N*-heptafluorobutyramide derivatives before analysis on a Hewlett-Packard 6890/5973 gas chromatograph/mass spectrometer. Isotope enrichment (percent) and tracer/tracee ratio (percent) were calculated from the observed ion current ratios (20). The isotopic enrichment of leucine in the apolipoproteins was expressed as tracer/tracee ratio (percent) using standarized formulas (20).

Kinetic analysis

The kinetics of apoB-100 in the VLDL, IDL, and LDL fractions were derived by a multicompartmental model previously described (21, 22), with each compartment representing a group of kinetically homogenous particles (Fig. 1). This simplified model has been compared with more complex multicompartmental models with two or more VLDL compartments (19, 23, 24) and was selected based on a statistically better fit of tracer/tracee ratio data. Briefly, compartment 1 represents the plasma amino acid pool. Compartment 2 is an intracellular delay compartment representing the synthesis of apoB in the liver. Compartment 3 represents plasma VLDL; compartment 4, IDL; and compartment 5, LDL. It is assumed that plasma leucine (compartment 1) is the source of the leucine that is incorporated into apoB and that all apoB enters plasma via compartment 3. Therefore, transport rates into compartment 3 correspond to total apoB-100 production. We also assumed a constant enrichment of the precursor pool and used the VLDL apoB-100 plateau tracer/tracee ratio data as the forcing function to drive the appearance of tracer into apoB-100 as previously described (19). In order to model LDL data, the LDL enrichment curve has been constrained to a value equivalent to the VLDL apoB-100-plateau enrichment at two distant time points (1900 and 2000 h). Under steady-state conditions, the fractional catabolic rate (FCR) is equivalent to the fractional synthetic rate. ApoB-100 production rates (PRs) were determined by the formula PR (mg·kg^{-1}·d^{-1}) =

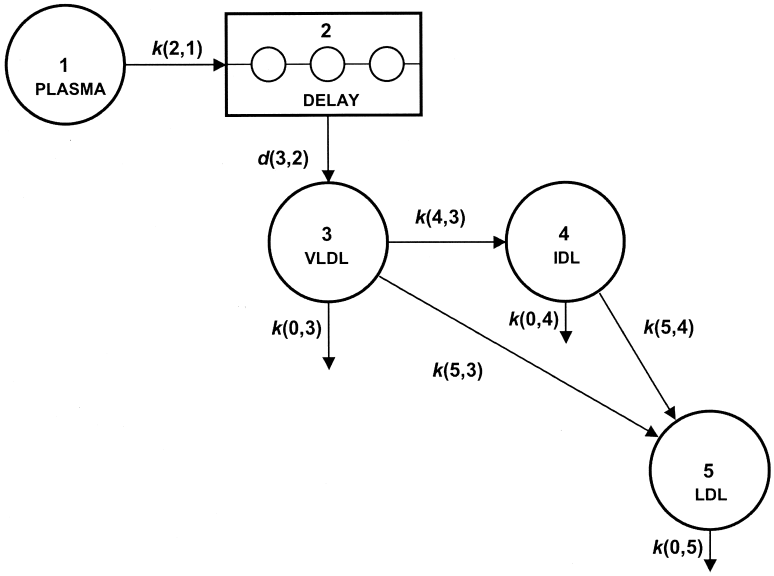

Fig. 1. Multicompartmental model for apoB-100 metabolism. Compartment 1 represents the plasma amino acid pool. Compartment 2 is an intracellular delay compartment representing the synthesis of apoB-100 and assembly of lipoproteins in the liver. Compartment 3 represents VLDL; compartment 4, IDL; and compartment 5, LDL.

[FCR (pools/d) × apoB concentration (mg/dl) × plasma volume (l)]/body weight (kg) (25). Plasma volume was estimated as 4.5% of body weight. The SAAM II program (SAAM Institute, Seattle, WA) was used to fit the model to the observed tracer data.

DNA analysis

The deletion >15 kb at the 5′ end of the LDL receptor gene was screened as previously described (12). Genotyping of apoE was done by PCR amplification of a 244 bp fragment of exon 4 of the apoE gene with oligonucleotides F4 and F6 and digestion of PCR fragments with the restriction enzyme *Hha*I (26).

Statistical analysis

Data from FH patients were compared with data from control subjects using nonparametric Wilcoxon test for continuous measures. All analyses were performed using JMP Statistical Software (version 5.01a, SAS Institute, Cary, NC).

RESULTS

Characteristics of the subjects

Table 1 shows the baseline characteristics of the subjects in the fasting state. As mentioned above, all FH subjects were carriers of the same null LDL receptor gene mutation and all participants were homozygotes for the apoE3 allele. No significant difference was observed between controls and FH subjects for age, weight, and BMI. FH heterozygotes had greater plasma concentrations of total cholesterol (135%; $P = 0.006$), VLDL-cholesterol (100%; $P = 0.01$), LDL-cholesterol (239%; $P = 0.006$), triglycerides (TGs) (75%; $P = 0.01$) and VLDL-TGs (60%; $P = 0.04$), and lower HDL-cholesterol levels (23%; $P = 0.01$) than controls. As compared with heterozygotes, the FH homozygote exhibited greater plasma levels of to-

TABLE 1. Baseline characteristics of the subjects

	Controls (n = 5) Mean ± SD; Range	FH HTZ (n = 6) Mean ± SD; Range	FH HMZ (n = 1) Mean	P^a
Age, y	24.7 ± 1.3 22–25	29.3 ± 9.9 19–45	16.9	0.6
Weight, kg	77.6 ± 8.3 68–86	69.8 ± 14.0 56–96.5	52.7	0.1
BMI, kg/m^2	23.9 ± 1.4 22.0–25.2	22.0 ± 4.3 18.6–30.5	22.0	0.1
Total cholesterol, mmol/l	4.0 ± 0.8 2.8–4.9	9.4 ± 1.9 6.8–12.6	15.5	0.006
VLDL-cholesterol, mmol/l	0.3 ± 0.2 0.09–0.5	0.6 ± 0.1 0.4–0.7	2.0	0.01
LDL-cholesterol, mmol/l	2.3 ± 0.6 1.7–2.8	7.8 ± 1.8 5.3–10.9	13.1	0.006
HDL-cholesterol, mmol/l	1.3 ± 0.3 0.9–1.7	1.0 ± 0.1 0.8–1.2	0.4	0.01
TG, mmol/l	0.8 ± 0.3 0.5–1.1	1.4 ± 0.2 1.1–1.6	3.6	0.01
VLDL-TG, mmol/l	0.5 ± 0.2 0.2–0.7	0.8 ± 0.2 0.5–0.9	1.5	0.04

BMI, body mass index; FH, familial hypercholesterolemia; HTZ: heterozygote; HMZ: homozygote; TG: triglyceride.

[a] P represents the P value for the difference between controls and FH heterozygotes.

TABLE 2. Nonfasting apolipoprotein concentrations

	Controls (n = 5) Mean ± SD; Range	FH HTZ (n = 6) Mean ± SD; Range	FH HMZ (n = 1) Mean	P^a
		mg/dl		
Total plasma apoB	85.4 ± 29.7 52.8–130.9	195.1 ± 27.6 150.7–236.5	334.7	0.006
VLDL apoB-100	6.0 ± 1.8 3.9–8.2	11.0 ± 2.8 7.0–15.0	23.9	0.02
IDL apoB-100	0.5 ± 0.2 0.3–0.8	1.2 ± 0.9 0.3–2.6	14.1	0.5
LDL apoB-100	78.4 ± 28.1 48.2–122.4	182.1 ± 25.1 142.2–220.3	294.4	0.006

[a] *P* represents the *P* value for the difference between controls and FH heterozygotes.

tal cholesterol (65%), VLDL-cholesterol (233%), LDL-cholesterol (68%), TGs (157%) and VLDL-TGs (88%), and lower HDL-cholesterol levels (60%).

The nonfasting concentrations of total plasma apoB and VLDL, IDL, and LDL apoB-100 obtained during the kinetic study are shown in **Table 2**. As expected, the total apoB levels were higher in FH subjects as compared with controls (heterozygotes = 128%; homozygote = 292%). The VLDL and LDL apoB-100 levels were also higher in FH subjects than in controls (heterozygotes = 83% and homozygote = 298% for VLDL apoB-100; heterozygotes = 132% and homozygote = 276% for LDL apoB-100). As compared with controls, IDL apoB-100 levels tended to be greater in FH heterozygotes (140%; $P = 0.5$), but this tendency did not reach statistical significance. Plasma concentrations of IDL apoB-100 were markedly elevated in the FH homozygote as compared with controls and heterozygotes.

Kinetics of VLDL, IDL, and LDL apoB-100

Analyses of deuterated plasma amino acids indicated that plasma leucine enrichments remained constant during the course of the infusion (data not shown). The mean VLDL, IDL, and LDL apoB-100 tracer/tracee ratios in control and FH subjects are shown in **Fig. 2**. **Table 3** shows the PSs, FCRs and PRs for apoB-100 for the control and FH subjects in the VLDL, IDL, and LDL fractions. As compared with controls, the VLDL apoB-100 PR was increased by 50% in FH heterozygotes (43.9 ± 10.8 vs. 29.2 ± 7.5 mg·kg^{-1}·d^{-1}; $P = 0.04$), and by 109% in the FH homozygote (61.1 vs. 29.2 ± 7.5 mg·kg^{-1}·d^{-1}). Moreover, the VLDL apoB-100 PS was increased by 63% and 164% in FH heterozygotes and the homozygote, respectively, but this difference did not reach statistical significance. Kinetic parameters for IDL apoB-100 were comparable between FH heterozygotes and controls, but the FH homozygote had a 18.3-fold higher IDL apoB-100 PS, a 6.8-fold lower IDL apoB-100 FCR and a 3.9-fold higher IDL apoB-100 PR than controls. As expected, FH heterozygotes had significantly higher LDL apoB-100 PS ($P = 0.02$) and lower LDL apoB-100 FCR ($P = 0.006$) than controls, but no significant difference was noted between the two groups for LDL apoB-100 PR. Finally, as compared with controls, the FH homozygote had a markedly elevated LDL apoB-100 PS and PR and a lower LDL apoB-100 FCR.

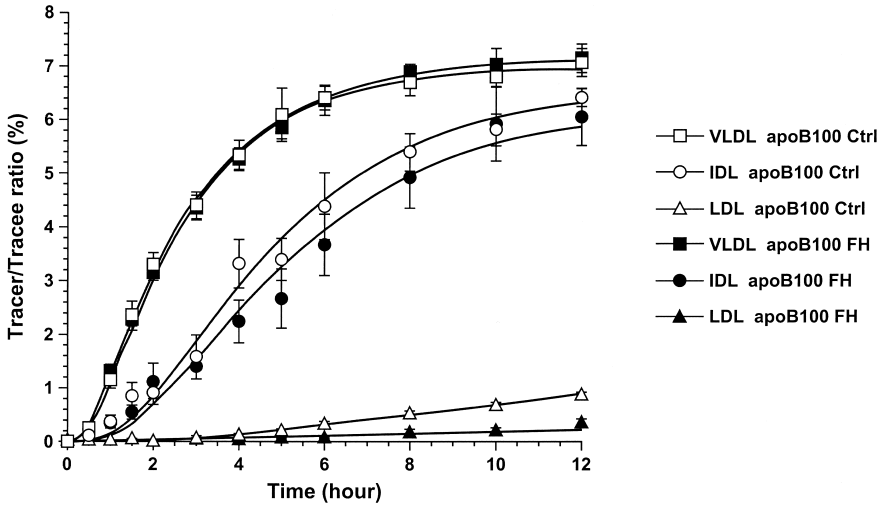

Fig. 2. ApoB-100 leucine tracer/tracee ratios for VLDL, IDL, and LDL in control and familial hypercholesterolemic subjects. Results are shown as mean ± SEM for both groups.

TABLE 3. PS, FCR, and PR of VLDL, IDL, and LDL apoB-100

	VLDL apoB-100			IDL apoB-100			LDL apoB-100		
	PS	FCR	PR	PS	FCR	PR	PS	FCR	PR
	mg	*pools/d*	*mg/kg^{-1}/d^{-1}*	*mg*	*pools/d*	*mg/kg^{-1}/d^{-1}*	*mg*	*pools/d*	*mg/kg^{-1}/d^{-1}*
Controls Mean ± SD (n = 5)	214.1 ± 83.9	11.3 ± 3.2	29.2 ± 7.5	18.3 ± 7.2	8.8 ± 2.5	2.1 ± 1.2	2,806 ± 1,264	0.4 ± 0.06	14.9 ± 6.3
FH HTZ Mean ± SD (n = 6)	349.4 ± 132.9	9.1 ± 2.0	43.9 ± 10.8	39.1 ± 35.1	7.4 ± 3.0	3.1 ± 2.1	5,814 ± 1,960	0.2 ± 0.1	13.5 ± 7.4
FH HMZ Mean (n = 1)	565.9	5.7	61.1	335.2	1.3	8.2	6982	0.2	30.5
P	0.1	0.3	0.04	0.6	0.5	0.4	0.02	0.006	0.7

FCR, fractional catabolic rate; PR, production rate; PS, pool size.
**P* represents the *P* value for the difference between controls and FH heterozygotes.

DISCUSSION

A number of in vitro studies have suggested that the LDL receptor may play a role in the regulation of the hepatic production rate of apoB-100-containing lipoproteins. Horton et al. (4) have demonstrated that primary hepatocytes from transgenic mice showed an increased apoB secretion in the absence of the LDL receptor. Similarly, Liao et al. (27) found that hepatocytes from LDL receptor-deficient (LDLR$^{-/-}$) mice secreted more apoB-100 than did hepatocytes from wild-type mice. An even stronger demonstration that functional LDL receptor plays a critical role in apoB-100 secretion was recently reported by Twisk et al. (5), who explored the relationship between the presence of the LDL receptor and lipoprotein secretion in hepatocytes from both wild-type and LDLR$^{-/-}$ mice. LDLR$^{-/-}$ hepatocytes secreted apoB-100 at a 3.5-fold higher rate than did wild-type hepatocytes, suggesting that the LDL receptor could alter the proportion of apoB-100 that escapes co- or posttranslational presecretory degradation. Moreover, Twisk et al. (5) reported that the apoB secretion by mouse primary hepatocytes was modulated by the presence of heparin in the culture medium and suggested that the LDL receptor could affect the production rate of apoB by promoting the uptake of newly secreted apoB-containing lipoproteins at the cell surface. Consequently, the model proposed by Twisk et al. would predict that the type of LDL receptor mutation will affect the rate of VLDL secretion. Functionally null mutations would result in higher VLDL secretion than functionally defective mutations, because defective LDL receptors could still associate with nascent apoB-100 and facilitate its removal from the endoplasmic reticulum or its degradation (28). This prediction is supported by studies of the Watanabe heritable hyperlipidemic (WHHL) rabbit, an animal model of homozygous FH in which LDL receptors stall in the endoplasmic reticulum but retain ligand binding capacity (29). VLDL secretion from perfused WHHL liver (30) or from cultured WHHL hepatocytes (31) is similar to that of wild-type rabbit liver and hepatocytes, respectively. In contrast, however, the model proposed by Twisk et al. is not supported by Millar et al. (32), who measured the in vivo production of VLDL apoB in wild-type mice and in mice lacking LDL receptors and/or *apobec1* activity after the injection of [^{35}S]methionine and the lipase inhibitor Triton WR1339. They reported that there was no difference in the production rate of VLDL apoB between wild-type mice and LDLR$^{-/-}$ mice and between LDLR$^{-/-}$ mice and LDLR$^{-/+}$ mice on an *apobec1*$^{-/-}$ background, suggesting that the LDL receptor has no effect on the production rate of VLDL apoB in mice.

Despite extensive animal studies, the presence of a direct link between functional LDL receptor expression and apoB-100 secretion has been studied in only a small number of human in vivo kinetic studies, which have generated conflicting results. Using a radiolabeling methodology, Soutar, Myant, and Thompson (8, 9) showed that the VLDL apoB production rate of FH homozygotes was not significantly different from that of heterozygotes and control subjects, indicating that the LDL receptor had no effect on apoB production. Similarly, a kinetic study of three receptor-negative FH homozygotes performed by Uauy et al. (33) suggested that hepatic production of apoB-containing lipoproteins was not significantly increased in these patients. In contrast to these studies, however, James et al. (34) reported that VLDL apoB production rates of FH homozygotes were significantly increased by 54% as compared with those of controls. Using a stable isotope labeling technique, Cummings et al. (10) found that the VLDL apoB-100 PS was significantly higher in FH heterozygotes than in controls due to a 442% higher VLDL apo100 PR. Zulewski et al. (11) reported a more modest increase (33%) in VLDL apoB-100 PR in FH heterozygotes as compared with controls. On the other hand, Fisher et al. (35) as well as Gaffney et al. (36) observed a lower VLDL apoB-100 PR in FH heterozygotes as compared with controls, but this difference was not significant. Discrepancies between the results of these studies could be related to a number of factors, including variations in ethnicity of the participants, sample sizes, FH phenotypes, and methodology. It is also likely that variability in metabolic factors, such as insulin resistance (37), the degree of functionality of the LDL receptor (38, 39) and apoE polymorphism could account, at least in part, for heterogeneity of the kinetics of VLDL apoB-100. In some instances, the diagnosis of FH was made on the basis of clinical criteria, and the nature of the molecular defect in

the LDL receptor gene remained undefined. Heterogeneity of the apoE genotype has also been shown to modulate apoB-100 kinetics. In a recent study, Welty et al. (40), have shown that, as compared with apoE3 homozygotes, subjects carrying the apoE3/E4 genotype had significantly higher LDL apoB-100 levels due to lower fractional catabolism of LDL apoB-100 and an increase in the conversion of VLDL apoB-100 to LDL apoB-100. Watts, Moroz, and Barrett (41) also showed that the FCR of VLDL apoB-100 was lower in carriers of an apoE4 allele. Finally, differences in the methods could also explain discrepancies between the results, because data were analyzed using various multicompartmental or noncompartmental models. In the present study, particular attention was given to including only male participants, except for the FH homozygote, and homozygotes for the apoE3 allele with a BMI between 20 and 30 kg/m^2. It is therefore unlikely that the influence of the null LDL receptor allele on apoB-100 kinetics could be attributed to heterogeneity of these parameters.

In the present study, we hypothesized that the elevated plasma levels of apoB-100-containing lipoproteins found in FH heterozygotes were partly explained by an increased hepatic production rate of VLDL apoB-100. The kinetics of apoB-100 were measured in five controls, six FH heterozygotes, and one FH homozygote carrying a deletion >15 kb at the 5′ end of the gene. The deletion >15 kb has been shown to impair the production of mRNA and is classified as a receptor-negative (null) mutation, because the LDL receptor protein is completely absent from the cell surface (42). The impact of this mutation on the clinical severity of the FH phenotype has been well characterized in homozygotes (38) and heterozygotes (43). Our results showed that this LDL receptor gene mutation was associated with an increase of VLDL apoB-100 PRs in both FH heterozygotes and the FH homozygote. Interestingly, we also noted that the IDL apoB-100 kinetic parameters were not significantly influenced by the presence of a single mutant LDL receptor allele, although there was a nonsignificant 2.1-fold increase in IDL apoB-100 PS in FH heterozygotes. The FH homozygote, however, exhibited a markedly elevated IDL apoB-100 PS, most probably related to a lowered IDL apoB-100 FCR as well as an increase in IDL apoB-100 PRs. These findings suggest that the low numbers of functional LDL receptors found in FH heterozygotes may be sufficient to attenuate the accumulation of remnant particles and support the concept that deficiency of LDL receptors could lead to an enhanced conversion of VLDL to LDL, which also contributes to the increased LDL apoB 100 PS in FH (44).

We conclude that the VLDL apoB-100 PR is increased in a set of well-characterized FH subjects carrying the same null LDL receptor gene mutation. These data indicate that the elevated plasma levels of apoB-containing lipoproteins found in FH subjects are related to both overproduction of VLDL apoB-100 and reduction in the LDL apoB-100 FCR. Further investigations including a large number of FH patients encompassing a wide range of functionality of the LDL receptor will be required to fully understand the role of the LDL receptor in the metabolism of apoB-containing lipoproteins in humans.

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