Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 5693–5697, September 1982
Medical Sciences

Delayed clearance of very low density and intermediate density lipoproteins with enhanced conversion to low density lipoprotein in WHHL rabbits

(animal model for familial hypercholesterolemia/deficient low density lipoprotein receptors/protein catabolism)

TORU KITA, MICHAEL S. BROWN, DAVID W. BILHEIMER, AND JOSEPH L. GOLDSTEIN

Departments of Molecular Genetics and Internal Medicine, University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235

Contributed by Michael S. Brown, June 24, 1982

ABSTRACT **Rabbit livers express two genetically distinct receptors for plasma lipoproteins: (*i*) the low density lipoprotein (LDL) receptor and (*ii*) the chylomicron remnant receptor. In homozygous Watanabe-heritable hyperlipidemic (WHHL) rabbits, an animal model for human familial hypercholesterolemia, LDL receptors are genetically deficient, but chylomicron remnant receptors are normal. Hence, WHHL rabbits clear LDL from the circulation at an abnormally slow rate, but they clear chylomicron remnants at a normal rate. The current studies show that WHHL rabbits clear ^{125}I-labeled very low density lipoprotein (VLDL) and its metabolic product, intermediate density lipoprotein (IDL), from plasma at a markedly decreased rate. The impaired clearance is due to a profound decrease in the rate of uptake of ^{125}I-labeled VLDL and ^{125}I-labeled IDL by the liver. Because of its rapid clearance in normal rabbits, only a fraction of the ^{125}I-labeled apoprotein B component of VLDL is converted to LDL. In WHHL rabbits, the impaired clearance of VLDL leads to a markedly increased conversion of ^{125}I-labeled apoprotein B from VLDL to LDL. These results indicate that: (*i*) in rabbits, the LDL receptor mediates the rapid removal of VLDL and IDL from plasma, and (*ii*), a deficiency of LDL receptors leads to an enhanced conversion of VLDL to LDL. The combination of overproduction and impaired plasma clearance of LDL, both resulting from a single gene mutation in the LDL receptor, leads to a massive increase of plasma LDL levels in homozygous WHHL rabbits.**

Recent studies have defined two genetically distinct receptor systems that remove lipoproteins from the circulation of the rabbit: (*i*) the low density lipoprotein (LDL) receptor (1) and (*ii*) the chylomicron remnant receptor (2). This distinction has emerged from comparison of the rates of clearance of radiolabeled lipoproteins from the circulation of normal rabbits and homozygous Watanabe-heritable hyperlipidemic (WHHL) rabbits, which have a genetic defect in the LDL receptor and, thus, are an animal model for human homozygous familial hypercholesterolemia (FH) (1–3). In WHHL rabbits, endogenous LDL accumulates to high levels in plasma, and the rate of removal of injected ^{125}I-labeled LDL (^{125}I-LDL) from the circulation is markedly decreased (1, 4). On the other hand, chylomicron remnants do not accumulate in plasma, and radiolabeled chylomicrons are removed from the circulation at a normal rate despite the deficiency of LDL receptors (2).

The functional deletion of the LDL receptor in the WHHL rabbit offers an opportunity to determine whether this receptor normally plays a role in the plasma clearance of very low density lipoprotein (VLDL) or of its metabolic product, intermediate density lipoprotein (IDL), or of both. The first step in VLDL metabolism is its interaction with lipoprotein lipase, which converts the triglyceride-rich VLDL to a cholesteryl ester-rich particle, designated IDL. The IDL particles have two metabolic fates: (*i*) they can be rapidly taken up and catabolized in the liver, or (*ii*) they can remain in the circulation where they undergo a further conversion to LDL (reviewed in ref. 5).

Circumstantial evidence suggests that IDL particles, like LDL, enter the liver by binding to LDL receptors. IDL particles, which are rich in apoprotein (apo) E and apo B, bind with high affinity to LDL receptors *in vitro* (5). The concentration of IDL is increased several fold in the plasma of WHHL rabbits (unpublished data; ref. 4) as it is in humans with homozygous FH (6), who also lack LDL receptors (5). In the FH homozygotes, this increase is caused by a delayed removal of IDL from plasma (6), presumably as a result of the deficiency of hepatic LDL receptors.

If IDL particles are not removed from the circulation at a normal rate in the absence of the LDL receptor, they might be converted to LDL in increased amounts, and this might contribute to the enhanced production of LDL observed previously in FH homozygotes (6, 7) and in WHHL rabbits (1). Therefore, the current studies were undertaken to determine whether WHHL rabbits have a delayed clearance of VLDL and IDL from plasma. For this purpose we injected ^{125}I-labeled VLDL intravenously into normal and WHHL rabbits and followed the metabolic fate of its apo B component. The results show a delayed clearance of the apo B of VLDL and IDL from the circulation and an enhanced conversion of the apo B component to LDL in the WHHL rabbit.

METHODS

Rabbits. New Zealand White rabbits ("normal" rabbits) were purchased from Hickory Hill Rabbitry (Flint, TX). Homozygous WHHL rabbits were raised in Dallas by mating heterozygous WHHL females with homozygous WHHL males (3, 8). The heterozygous females were obtained by mating normal female rabbits with homozygous WHHL rabbits. Animals were fed Purina rabbit laboratory chow and were age 3–5 months (2–3.6 kg of body weight) at the time of study.

Lipoproteins. Plasma VLDL (density, <1.006 g/ml), IDL (density, 1.006–1.019 g/ml), LDL (density, 1.019–1.063 g/ml), and high density lipoprotein (HDL) (density 1.125–1.215 g/ml) were isolated by sequential ultracentrifugation (9). β-VLDL (density <1.006 g/ml) was isolated from the plasma of cholesterol-fed rabbits (10). VLDL was radioiodinated by using

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Abbreviations: apo, apoprotein(s); FH, familial hypercholesterolemia; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; WHHL rabbit, Watanabe-heritable hyperlipidemic rabbit; ^{125}I-LDL, ^{125}I-VLDL, ^{125}I-apo-B, ^{125}I-labeled LDL, VLDL, and apo B, respectively.

iodine monochloride (11), dialyzed against buffer containing 0.15 M NaCl and 0.01% EDTA (pH 7.4), and passed through an 0.45-μm filter (Millipore). Specific activity for ^{125}I-labeled VLDL (^{125}I-VLDL) was 6–13 × 10^5 cpm/μg of protein. Of the total radioactivity in ^{125}I-VLDL, 10% was extractable into chloroform/methanol.

Intravenous Injection of ^{125}I-VLDL and Measurement of Tissue Content of ^{125}I Radioactivity. Normal and WHHL rabbits, matched for weight and sex, were anesthetized, a catheter was inserted into the internal jugular vein (1), and the animals were allowed to recover for 48–72 hr before study. In some cases, animals were fasted for 16–24 hr prior to study (see legends to Figs. 1–3). ^{125}I-VLDL was mixed with 1 ml of autologous rabbit plasma and injected into the marginal ear vein. Blood samples (6 ml) were obtained from the indwelling catheter at the indicated times. Animals were kept in restraining cages for the first 2 hr and then returned to their cages with free access to food and water. The 100% value for plasma ^{125}I radioactivity was determined by dividing the total amount of injected ^{125}I-VLDL radioactivity by the plasma volume, calculated by the following formula: plasma volume (ml) = body weight (kg) × $57 \times \frac{(100 - \text{hematocrit})}{100}$, where 57 represents the blood volume in ml per kg of body weight (12). Two minutes after injection, the calculated values for total ^{125}I radioactivity remaining in plasma averaged 91% and 107% of the injected dose for normal and WHHL rabbits, respectively. In experiments in which tissues were obtained, the animals were anesthetized and perfused *in situ* with 0.15 M NaCl/1 mM $CaCl_2$ for 3 min through the portal vein (10). Various organs were then removed, and either 1-g pieces or the entire organ (spleen and adrenal gland) was assayed for ^{125}I radioactivity.

The content of ^{125}I-labeled apo B (^{125}I-apo B) in plasma VLDL, IDL, and LDL after injection of ^{125}I-VLDL was measured after isopropanol precipitation of the isolated lipoproteins as described by Holmquist *et al.* (13), followed by scintillation counting of the isopropanol-insoluble ^{125}I-apo B.

Electrophoresis. NaDodSO$_4$/polyacrylamide gel electrophoresis was conducted in 10% slab gels (14). Samples of VLDL, IDL, and LDL were delipidated by extraction with acetone/ethanol, 1:1 (vol/vol), at −20°C. The apoprotein precipitate was dissolved in buffer containing 10% glycerol, 5% 2-mercaptoethanol, 2.3% NaDodSO$_4$, and 62.5 mM Tris·HCl (pH 6.8) (15) after heating at 90°C for 3 min. Electrophoresis was carried out at 30 mA per gel at 4°C for 3 hr. Autoradiograms were prepared by exposing dried gels to Kodak XAR-5 film at −70°C in the presence of Cronex Lightning-Plus intensifying screens (16). Agarose gel electrophoresis of native lipoproteins was carried out as described (17).

RESULTS

The concentration of apo B in each plasma fraction of density <1.063 g/ml was increased in WHHL rabbits as compared with normal rabbits (VLDL, 25 vs. 10 mg/dl; IDL, 64 vs. 7 mg/dl; and LDL, 168 vs. 16 mg/dl) (unpublished data). The mass ratio of cholesterol to protein was increased in VLDL of WHHL rabbits as compared with normals (2.2 vs. 1.0). Conversely, the mass ratio of triglyceride to protein was decreased in VLDL of WHHL rabbits as compared with normals (3.6 vs. 6.6). These measurements were made in collaboration with R. J. Havel and will be reported elsewhere. When VLDL was radiolabeled with ^{125}I and subjected to NaDodSO$_4$ electrophoresis, the ratios of ^{125}I radioactivity in apo B, E, and C were similar in VLDL from normal (62:9:29) and WHHL (70:7:23) rabbits. The VLDL that accumulated in WHHL rabbits showed pre-β mobility on agarose gel electrophoresis; this mobility was distinctly faster than that of β-VLDL, a cholesteryl ester-rich VLDL that accumulates in the plasma of cholesterol-fed animals (Fig. 1).

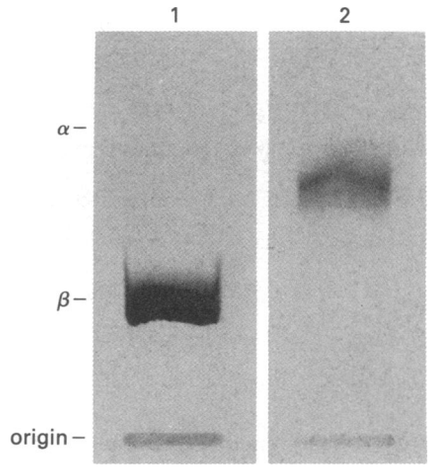

FIG. 1. Agarose gel electrophoresis. Aliquots (≈25 μg of protein) of β-VLDL from a cholesterol-fed rabbit (*lane 1*) and VLDL from a 24-hr fasted WHHL rabbit (*lane 2*) were subjected to agarose gel electrophoresis and stained with Fat Red 7B.

Fig. 2 shows a series of experiments in which ^{125}I-VLDL was injected intravenously into paired normal and WHHL rabbits, and the disappearance of total ^{125}I radioactivity from the plasma was measured. In all experiments, the clearance of ^{125}I in WHHL rabbits was markedly delayed in comparison with the normal rabbits. This was true when the injected ^{125}I-VLDL was obtained from any one of the following sources: (*i*) from fasted normal rabbits (Fig. 2*A*; time for 50% decline in plasma radioactivity or half-time, 1 hr and 9 hr for normal and WHHL recipient rabbits, respectively); (*ii*) from fed WHHL rabbits (Fig. 2*B*; half-time, 12 min and 4 hr for normal and WHHL recipients, respectively); or (*iii*) from fasted WHHL rabbits (Fig. 2*C*; half-time, 40 min and 10 hr for normal and WHHL recipients, respectively). The delayed VLDL clearance in WHHL rabbits

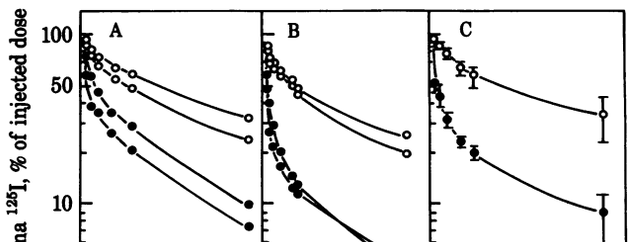

FIG. 2. Disappearance of total plasma ^{125}I radioactivity after intravenous injection of ^{125}I-VLDL in normal (●) and WHHL (○) rabbits. (*A*) Recipient male animals (2 normal, 2 WHHL) were fasted 16 hr prior to the injection of ≈2.3 × 10^8 cpm of ^{125}I-VLDL prepared from normal 24 hr-fasted rabbits. (*B*) Fed recipient male animals (2 normal, 2 WHHL) received ≈3 × 10^8 cpm of ^{125}I-VLDL prepared from fed WHHL rabbits. (*C*) Fed recipient animals (3 normal, 4 WHHL) received ≈2.9 × 10^8 cpm of ^{125}I-VLDL prepared from 24-hr-fasted WHHL rabbits. Two of the three normal recipient rabbits were female and one was male; two of the four WHHL recipient rabbits were female and two were male. In *A* and *B*, each curve represents a single animal. In *C*, the mean ± range of three normal or four WHHL animals is shown. The earliest time point shown is 30 min after injection. The values at 2 min after injection (see *Methods*) are not shown.

Table 1. Tissue distribution of ^{125}I after intravenous injection of ^{125}I-VLDL in normal and WHHL rabbits

	^{125}I-VLDL, % of injected dose per tissue	
	Normal	WHHL
Plasma	30, 32	60, 60
Organs		
Liver	34, 32	3.4, 4.0
Spleen	0.09, 0.07	0.04, 0.05
Lungs	0.7, 0.6	0.8, 0.7
Kidneys	1.1, 1.2	1.5, 1.1
Small intestine	0.4, 0.6	0.6, 0.8
Adrenal glands	0.03, 0.03	0.005, 0.004

Recipient male animals (fed) were injected intravenously with ^{125}I-VLDL (4–12 × 10^7 cpm) prepared from WHHL rabbits that had been fasted for 24 hr. After 30 min, animals were killed and the ^{125}I radioactivity in the indicated tissues was measured. Each value represents the data from one animal.

was apparent whether the recipient animals were fasted (Fig. 2*A*) or fed (Fig. 2 *B* and *C*).

The delayed clearance of ^{125}I-VLDL from WHHL rabbit plasma was attributable to a failure of uptake of ^{125}I radioactivity by the liver (Table 1). Thirty minutes after injection of ^{125}I-VLDL into normal animals, 33% of the injected radioactivity was present in the liver; in the WHHL rabbits, <4% was present in the liver. The adrenal gland of the WHHL rabbits also took up only 1/6th as much ^{125}I as did that of the normal animal. The amount of ^{125}I in other organs was small and similar in normal and WHHL rabbits.

The movement of ^{125}I-apo B from VLDL to IDL and LDL after injection of ^{125}I-VLDL was followed by two methods. In one method, plasma was fractionated by ultracentrifugation, and uniform volumes of the VLDL, IDL, and LDL fractions were subjected to $NaDodSO_4$ electrophoresis. The ^{125}I-apo B band was visualized by autoradiography. Fig. 3 shows a representative experiment comparing one normal and one WHHL rabbit. In the normal rabbit, ^{125}I-apo B had largely disappeared from the VLDL fraction by 2 hr. The amount of ^{125}I-apo B in IDL was highest at the earliest time point studied (2 min) and thereafter declined rapidly. Only trace amounts of ^{125}I-apo B were seen in LDL. The results in the WHHL rabbit were strikingly different. The ^{125}I-apo B declined very slowly from VLDL; even after 25 hr, appreciable amounts were still present. The amount of ^{125}I-apo B in IDL of the WHHL rabbit increased

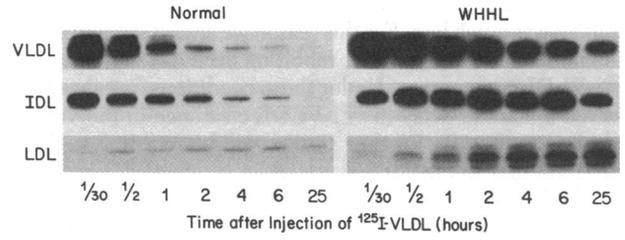

FIG. 3. Autoradiograms of $NaDodSO_4$/polyacrylamide gels showing the changes in the distribution of ^{125}I-apo B among plasma VLDL, IDL, and LDL after intravenous injection of ^{125}I-VLDL into normal and WHHL rabbits. One normal rabbit and one WHHL rabbit (fed) were injected with ≈2.9 × 10^8 cpm of ^{125}I-VLDL prepared from a 24-hr-fasted WHHL rabbit. At the indicated times, blood (6 ml) was obtained, and the plasma was subjected to sequential ultracentrifugation. Aliquots of VLDL (17 μl), IDL (17 μl), and LDL (5 μl) were delipidated, dissolved in $NaDodSO_4$ buffer, and subjected to electrophoresis and autoradiography. Gels were exposed for 17 hr for ^{125}I-VLDL and ^{125}I-labeled IDL and 3 days for ^{125}I-LDL. The bands corresponding to ^{125}I-apo B were cut from the gels and photographed.

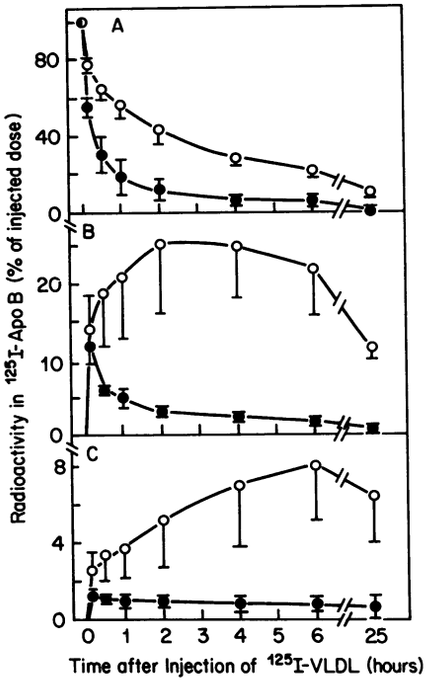

FIG. 4. Fate of ^{125}I-labeled apo B after intravenous injection of ^{125}I-VLDL (≈2.9 × 10^8 cpm) from 24-hr fasted WHHL rabbits into normally fed rabbits—three normal (●) and four WHHL (○)—as in Fig. 2*C*. At the indicated time, blood was obtained and the plasma was subjected to sequential ultracentrifugation. The ^{125}I-apo B content of the VLDL (*A*), IDL (*B*), and LDL (*C*) fractions was determined by isopropanol precipitation and is expressed as the mean percentage ± SEM of the ^{125}I-apo B present in the original VLDL. The values were not corrected for procedural losses, which averaged 5–10% for each lipoprotein fraction.

slowly to a peak at 4–6 hr and declined only partially at 25 hr. The amount of ^{125}I-apo B in LDL of the WHHL rabbit increased continually up to 6 hr and remained high at 25 hr.

To quantify the ^{125}I-apo B, aliquots of each lipoprotein fraction were subjected to extraction with isopropanol, a procedure that solubilizes all apoproteins other than apo B (13). The isopropanol-insoluble ^{125}I-labeled material was measured by scintillation counting. Fig. 4 shows the mean results of these measurements performed in three normal and four WHHL rabbits, all of which were injected with ^{125}I-VLDL isolated from WHHL animals (same animals as in Fig. 2*C*). In the WHHL rabbits, the decrease in ^{125}I-apo B in VLDL was markedly delayed as compared with the normal rabbit (Fig. 4*A*). The radioactivity in the IDL fraction increased progressively for 2 hr in WHHL rabbits and then declined extremely slowly. In normal animals, the IDL radioactivity declined rapidly from zero time (Fig. 4*B*). After 2 hr, 25% of the injected ^{125}I-apo B was present in the IDL fraction in WHHL rabbits as compared to 3% in normal rabbits. In WHHL rabbits, the amount of ^{125}I-apo B in LDL increased for 6 hr and attained a value of 8% of the injected dose (Fig. 4*C*). In normal rabbits, the amount of ^{125}I-apo B in LDL was small (1–2% of the injected dose) at all time points. These quantitative results were consistent with qualitative results observed with $NaDodSO_4$ gel electrophoresis (Fig. 3).

Table 2 shows the distribution of ^{125}I-apo B 6 or 7 hr after injection of various ^{125}I-VLDL preparations into normal and WHHL rabbits. Although there was variability among these three experiments, in each case the WHHL animals retained 2.5- to 5.5-fold more total ^{125}I-apo B in the circulation and accumulated 2.5- to 9-fold more ^{125}I-apo B in LDL than did the normal animals. In experiment C of Table 2, the recipient an-

Table 2. Fate of ^{125}I-apo B 6 or 7 hr after intravenous injection of ^{125}I-VLDL into normal and WHHL rabbits

Exp.	VLDL donor*	Lipoprotein fraction	% of injected dose	
			Normal	WHHL
A	WHHL	Total	9.4	52
		VLDL	6.7	22
		IDL	1.8	22
		LDL	0.9	8.0
B	Normal	Total	7.8	30
		VLDL	2.3	10
		IDL	2.5	13
		LDL	3.0	7.1
C	Normal	Total	27	62
		VLDL	3.0	4.6
		IDL	11	22
		LDL	13	35

Experiments: A, recipient normal (n = 3) and WHHL (n = 4) rabbits (fed) were injected with $\approx 2.9 \times 10^8$ cpm of ^{125}I-VLDL prepared from 24 hr-fasted WHHL rabbits (same experiment as in Fig. 2*C* and Fig. 4); B, recipient normal (n = 2) and WHHL (n = 2) rabbits were fasted 16 hr prior to the injection of $\approx 2.3 \times 10^8$ cpm of ^{125}I-VLDL prepared from 24 hr-fasted normal rabbits (same experiment as in Fig. 2*A*); C, recipient normal (n = 2) and WHHL (n = 2) rabbits (all female and fed) were injected intravenously with $\approx 2.6 \times 10^8$ cpm of ^{125}I-VLDL prepared from 24 hr-fasted normal rabbits. Blood was obtained 6 (experiments A and C) or 7 hr (experiment B) after injection of ^{125}I-VLDL, and the plasma was subjected to sequential ultracentrifugation. The ^{125}I-apo B content of each lipoprotein fraction was measured by isopropanol precipitation and is expressed as a percentage of the ^{125}I-apo B present in the original ^{125}I-VLDL. The values were not corrected for procedural losses, which averaged 5–10% for each lipoprotein fraction. Each value shown is the average of data obtained from the indicated number of animals.
* All fasted 24 hr.

imals were fed, and the clearance of normal ^{125}I-VLDL appeared delayed as compared with that in the fasted recipients (Table 2, experiment B). Nevertheless, the WHHL rabbits still showed a markedly decreased removal of ^{125}I-apo B from the circulation and an increased conversion to LDL.

DISCUSSION

The current studies demonstrate that the apo B component of ^{125}I-VLDL is removed from the circulation at an extremely slow rate in WHHL rabbits as compared with normal rabbits. Six hours after the injection of ^{125}I-VLDL (from WHHL rabbits) into normal rabbits, a total of only 9.4% of the injected ^{125}I-apo B remained in the plasma (6.7% in VLDL, 1.8% in IDL, and 0.9% in LDL). On the other hand, in the WHHL rabbit, 52% of the ^{125}I-apo B remained in the plasma at the same time point (22% in VLDL, 22% in IDL, and 8% in LDL) (Fig. 2; Table 2, experiment A). A markedly decreased removal of ^{125}I-apo B was also seen in WHHL rabbits when ^{125}I-VLDL from normal rabbits was injected (Fig. 2; Table 2, experiments B and C). The delayed clearance of the ^{125}I-apo B in WHHL rabbits was due to a marked decrease in hepatic uptake of radioactivity (Table 1).

These results strongly imply that VLDL or IDL, or both, enter the normal rabbit liver by binding to the LDL receptor. Even though the chylomicron remnant receptor functions normally in WHHL rabbits (2), it does not mediate normal clearance of plasma VLDL and IDL. It is striking that the lipoproteins that are cleared by the LDL receptor (i.e., LDL, VLDL, and IDL) all contain the high molecular weight form of apo B, so-called B-100 (unpublished data). On the other hand, chylomicron remnants, which are cleared by a different receptor, contain the low molecular weight form of apo B, B-48 (unpublished data). Yet, chylomicron remnants, VLDL, and IDL all contain apo E. It is difficult to escape the conclusion that the B-48 of chylomicron remnants plays a role in directing these particles to the chylomicron remnant receptor. It may do so by interacting with apo E in such a way as to facilitate binding to the remnant receptor.

Previous studies of the turnover of ^{125}I-LDL have suggested a 5-fold overproduction of LDL apo B in WHHL rabbits as compared with normals (1). In the current studies, we observed that an increased proportion of injected ^{125}I-VLDL was converted to ^{125}I-LDL in WHHL rabbits, thus causing an apparent LDL overproduction. This increased conversion apparently occurred as a consequence of the failure of hepatic clearance of ^{125}I-VLDL and IDL. From the current data, it is not possible to determine how much of the LDL overproduction in WHHL animals is attributable to the failure of hepatic clearance of VLDL and IDL with subsequent conversion into LDL and how much is due to excess *de novo* secretion of LDL. ^{125}I-VLDL consists of a heterogeneous mixture of particles of varying catabolic rates. This heterogeneity does not interfere with simple measurements of the percentage conversion of the ^{125}I-apo B to various lipoproteins. However, the translation of these observed isotopic values into absolute rates of production and catabolism of apo B requires knowledge of the specific radioactivity of apo B within each of the functionally heterogeneous lipoprotein fractions. Simple measurements of the specific activity of ^{125}I-apo B in each density class may be inadequate because the specific radioactivity of different particles within each class will differ if their rate of turnover differs. A minor fraction of VLDL that was rapidly converted to LDL might make a large contribution to LDL production, but its existence would be missed because one can measure only the mean rate of conversion of the whole VLDL pool. Because the specific activities cannot be computed, we cannot use the current data to calculate the absolute secretion rates of VLDL, IDL, or LDL. In studies of the metabolism of ^{125}I-VLDL in normal rabbits, Ghiselli recently concluded that VLDL was not an important source of LDL (18). Although our data are qualitatively similar to that of Ghiselli, we do not yet feel justified in making this conclusion because of the uncertainty about the specific activities of the various lipoproteins.

In these experiments, we noted a significant variation in the rates at which ^{125}I-VLDL was metabolized in different animals on different days. On any given day when animals were injected with the same ^{125}I-VLDL preparation, the variability between animals was much less. For this reason we always studied at least one normal and one WHHL rabbit on each day with the same ^{125}I-VLDL preparation. Under these conditions, we always observed a marked delay in ^{125}I-VLDL clearance in the WHHL rabbits (see Fig. 2). Further studies will be required to determine whether the day-to-day variation is due to differences in the ^{125}I-VLDL preparations or differences in physiologic states of the recipient animals (fed vs. fasted, male vs. female, etc.).

Whether the current observations on VLDL metabolism in rabbits are relevant to VLDL metabolism in humans is not yet certain. Similar experiments in humans with homozygous FH have been performed recently by Soutar *et al.*, who observed that the fractional rate of catabolism of IDL averaged only 1/6th of the normal value in four FH homozygotes after injection of ^{125}I-VLDL (6). These findings are remarkably similar to those in the WHHL rabbit, and they imply that the LDL receptor may play a role in the hepatic uptake of IDL in man as well as in the rabbit.

If the LDL receptor in fact does mediate the hepatic uptake

of VLDL and IDL, then a metabolically unstable condition exists with regard to control of plasma LDL levels in normal subjects as well as in FH patients (19). A decrease in the number of LDL receptors would lead to an enhanced conversion of IDL to LDL and, hence, an overproduction of LDL. At the same time, LDL catabolism would be retarded. Thus, a genetic or acquired deficiency of LDL receptors would lead simultaneously to both an overproduction and a delayed clearance of LDL, a combination that could produce a marked increase in plasma LDL levels.

James R. Ingram, Richard Gibson, and G. Michael Funk provided excellent technical assistance. This research was supported by grants from the National Institutes of Health (HL-20948 and HL-15949) and the Moss Heart Fund.

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