Plasma Cholesterol Transport in Anhepatic Rats

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Abstract

The plasma appearance of newly synthesized cholesterol in anhepatic laboratory diet-fed rats was 10% of the intact rat. In intact rats this cholesterol was mainly ester in lower density lipoproteins, but for anhepatic rats it was virtually only free in high density lipoprotein. Chylomicron cholesterol ester was removed much more slowly from anhepatic than control plasma and returned primarily as free in high density lipoproteins, with the control return 10 times the anhepatic return. Lower density lipoprotein cholesterol ester transfer to an extravascular pool in anhepatic rats was < 10% of controls. The liver was responsible for 95% of the extravascular lower density lipoprotein ester pool and only 50% of the for high density lipoprotein ester. Despite decreased anhepatic lipoprotein catabolism, the mass of both plasma low and high density lipoproteins progressively decreased indicating an even greater decrease in influx. The anhepatic fractional catabolic rate of apo A1 was similar to controls, but that of apo E was considerably less. Despite the unchanged catabolism of apo A1 and the reduced catabolism of apo E, plasma apo A1 decreased less than apo E after hepatectomy. The anhepatic data confirm the pivotal role of the liver in maintaining plasma low and high density lipoprotein cholesterol concentrations. They suggest that, in addition to its anabolic and catabolic functions, the liver also acts as a reservoir buffering changes in plasma concentration. (*J. Clin. Invest.* 1992. 89:1564–1570.) Key words: apoproteins • cholesterol • hepatic lipoprotein reservoir • plasma lipoprotein decrease

Introduction

The liver is recognized as the main organ responsible for plasma lipoprotein cholesterol homeostasis (1, 2). The presence of low density lipoprotein (LDL) receptors is considered (2) to be central to the control of the plasma concentration of LDL cholesterol. Enteral cholesterol is also processed in the liver after retrieval by the remnant uptake system (3, 4). This, subsequently, affects plasma cholesterol content primarily by regulating hepatic LDL receptor activity (5). Substantial information exists on the hepatic regulation of lipoprotein catabolism. However, comparatively fewer data have been developed on regulation of hepatic lipoprotein secretion or the role of the liver in lipoprotein interconversion.

Hepatectomy has been used (6) to obtain chylomicron remnants, but because of the brief postoperative survival, the model has had limited use in lipoprotein studies. 1 h after functional hepatectomy, decreases in plasma triglyceride-rich lipoproteins and increments in LDL and HDL cholesterol and apolipoprotein (apo) E were observed (7). The presence of necrotic viscera in situ with potential plasma contamination makes interpretation of these data difficult. A hepatectomy model (8) that entails removing the liver while preserving the remaining splanchnic viscera results in survivals in days rather than hours. This model permits longer-term evaluations of anhepatic plasma cholesterol transport. Comparing this anhepatic data with that of the intact rat provide insights into the role of the liver in plasma lipoprotein cholesterol transport and are presented here.

Methods

Chemicals and radiochemicals. [5-^{3}H]- and [2-^{14}C]RS mevalonolactone was purchased from Dupont-New England Nuclear (Boston, MA). [1,2^3-H]cholesterol and [4-^{14}C]cholesterol oleate were obtained from Research Products International (Mt. Prospect, IL). ^{125}I employed for the lipoprotein and bovine serum albumin iodination was obtained from Amersham Corp. (Chicago, IL). The lipids given by the enteral route to produce chylomicrons (i.e., oleic acid, monolein, triolein) were obtained from Sigma Chemical Co. (St. Louis, MO). All organic solvents employed in the extractions and assays were analytical reagent grade.

Animal procedures. All rats were male Sprague Dawley obtained from Charles River Breeding Laboratories, Inc. (Raleigh, NC) weighing between 240 and 350 g. The rats were maintained on standard rat laboratory diet and diurnal lighting. They were fasted from 6 to 12 h the night before the removal of the liver. The hepatectomy was performed by a method previously described from this laboratory (8), which involved the insertion of a prosthesis between the portal vein and vena cava in a one-stage procedure removing the entire liver. An intraarterial line was inserted with glucose and albumin infusions provided to avoid hypoglycemia (8). Radiolabeled substrates of cholesterol ester–labeled chylomicrons, LDL (*d* 1.006–1.063) or HDL (*d* 1.063–1.21), ^{125}I-apolipoproteins, or mevalonolactone were injected by this line usually at 2 h after surgery, and sequential blood samples were obtained. Both control and anhepatic rats were maintained in restraint during those studies. At the conclusion of the studies, plasma and tissues (skeletal muscle, heart, adipose, lung, spleen) were obtained for radiolabel assay.

Chylomicrons were obtained from the intestinal lymphatics of standard laboratory diet-fed rats by the method of Bollman et al. (9). A mixture of 50 mg of triolein, 25 mg of monolein, and 25 mg of oleic acid containing 5–10 μCi [4-^{14}C]cholesterol was infused into the duodenal cannula and the intestinal lymph was drained overnight at 4°C. The chylomicrons were incubated with red cell ghosts to minimize their content of radiolabeled free cholesterol, and the depleted chylomicrons were used on the same day of their collection.

Lipoprotein and apoprotein preparation. Chylomicrons were isolated from the intestinal lymph by a 1×10^6 *g*-min centrifugation at *d* 1.006 employing a model L5-65 ultracentrifuge (Beckman Instruments, Inc., Palo Alto, CA) and a Ti60 rotor. LDL were obtained from rat serum at $d < 1.063$ and 1×10^8 g-min after removing chylomicrons as described. HDL were isolated at *d* 1.063–1.21 and 2×10^8 g-min. Both lipoproteins were isolated from standard laboratory diet-fed rats

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previously injected (7 d) with [1,2-^{3}H]cholesterol. The isolated lipoproteins were dialyzed against 0.14 M NaCl, 0.02 M PO_4 (pH 7.4) (PBS) and then incubated with red blood cell ghosts with repeated changes to minimize the ^{3}H in free cholesterol. The HDL were applied to a heparin sepharose (Sigma Chemical Co.) column as described (10) to obtain the unbound (A1-HDL) fraction containing little apo E. The bound HDL were lyophilized and delipidated with 3:1 ethanol/diethyl ether. The apoproteins were then dissolved in PBS and applied to heparin sepharose to isolate apo E and apo A1. Both of these apolipoproteins and bovine serum albumin were iodinated with ^{125}I using the modified iodine monochloride method (11). The iodinated apolipoproteins and albumin were extensively dialyzed against PBS and the apolipoproteins checked for tracer distribution in an SDS polyacrylamide system (12). If > 3% of tracer was distributed in areas other than the protein mass, the labeled apoprotein was repurified. The iodinated apoproteins were added to 1 ml of rat plasma before arterial injection.

Chemical and radiochemical analysis. Plasma was extracted by the Dole techniques (13) in all studies evaluating plasma radiolabeled cholesterol content. Free cholesterol was separated from cholesterol ester by thin-layer chromatography on silica gel G using heptane-diethyl ether-glacial acetic acid (80:20:1). The bands were identified by brief I_2 exposure, removed, and eluted with 1:1 ethanol-diethyl ether and radioassayed in 0.5% diphenyloxazole in toluene. On each thin-layer plate a standard tracer cholesterol-cholesteryl oleate was run to determine recovery. This was always > 87% for each compound. Radioassay was done in a model LS8100 liquid scintillation spectrophotometer (Beckman Instruments, Inc., Irvine, CA). Plasma ^{125}I was assayed in the 10% trichloroacetic acid precipitate in a TRICARB model 4530 γ counter (Packard Instrument Co., Inc., Donners Grove, IL).

The plasma free cholesterol mass assay was performed either by a colorimetric method (14) or with an enzymatic technique (Wako Chemicals, Richmond, VA). Total cholesterol was assayed either with the procedure of Abell et al. (15) or with an enzymatic system (Wako Chemicals). Protein assays were performed by the Lowry method (16) and phospholipids by the Bartlett (17) colorimetric assay of phosphorous in the digested lipid extract. Along with ultracentrifugation, heparin manganese precipitation (18) was used to isolate the HDL from LDL.

Calculations. Kinetic analysis of the LDL and HDL [^{3}H]cholesterol ester used a two-pool model to simulate the two-exponential function. A plasma compartment from which catabolism (or transfer to a slow turnover pool) occurred and an extravascular pool from which no catabolism occurred. The same model was used for the ^{125}I-apo E and apo Al studies. The simulation was done with a SAAM 29 (19) program on a UNIX PC. Means of the data and standard errors were determined by routine methods (20). Significance evaluations of data used a one-sided *t* test (20).

Results

After the arterial injection of either 15 μCi of RS[5-^{3}H]-mevalonolactone or 5 μCi of RS[2-^{14}C]mevalonolactone into intact rats, a prompt appearance in plasma radiolabeled cholesterol was observed for the HDL and LDL (Fig. 1 *a*). Most of the cholesterol in both lipoproteins appeared as ester (Fig. 2). Similar injections into anhepatic rats (Fig. 1 *b*) produced plasma cholesterol activities which were 10–15% that of intact rats, with virtually all of the tracer found in HDL-free cholesterol (Fig. 2).

The clearance of chylomicron [^{14}C]cholesterol (79% cholesterol ester) from the plasma of intact rats occurred promptly (Fig. 3 *a*) with a gradual return of the tracer mainly in the heparin-manganese supernate or HDL fraction. The peak of this return coincided with a maximum of tracer-free cholesterol (Fig. 4) at ~ 6 h. The anhepatic rat had a very slow clearance of chylomicron cholesterol ester (Fig. 3 *b*) with much less

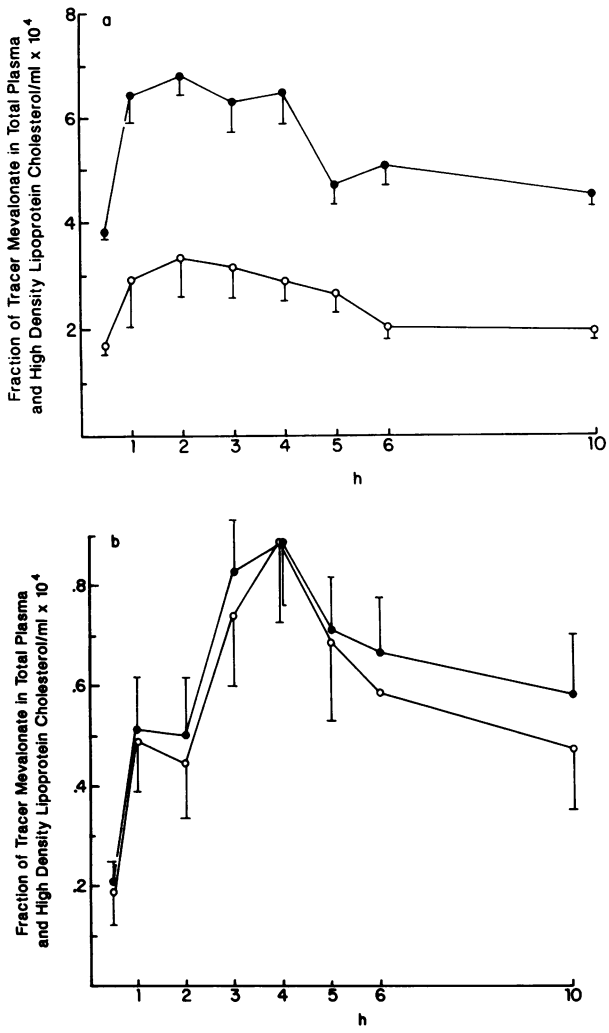

Figure 1. (*a*) The fraction of radiolabeled [2-^{14}C]RS mevalonate 2 μCi (< 0.5 nmol) incorporated into total (●) and HDL (○) plasma cholesterol after arterial injection of the precursor into intact rats. The data are the mean±SE of five rats. (*b*) The same data (mean±SE, n = 5) in anhepatic rats.

return of [^{14}C]cholesterol in HDL and significantly less as free cholesterol (Fig. 4).

The initial decay of LDL (d = 1.006–1.063) [1,2-^{3}H]-cholesterol ester (86±5% ester, n = 5) was quite different between the intact and anhepatic rats (Fig. 5 *a*). The prompt decrease in early activity observed in the intact rat was not seen without the liver. The difference in the second exponential of these two functions was not as pronounced. The plasma decay of Al-HDL (d = 1.063–1.21; heparin sepharose unbound) cholesterol ester (89±8% ester, n = 4) was somewhat slower (Fig. 5 *b*) for the anhepatic than the control, but this difference was not as great as the LDL (d = 1.006–1.063) cholesterol. The decay data were modeled by a two-compartment system (Fig. 6) assuming that the plasma lipoprotein ester equilibrates with an extravascular pool. Although the fractional transfer rate to the extravascular pool (Table I, L_E) and the fractional removal rate (L_O) were lower for the anhepatic HDL cholesterol ester than control, the differences were not significant. These respective rates for LDL cholesterol ester in the anhepatic rats (Table I) were significantly less than the intact rats, with the fractional

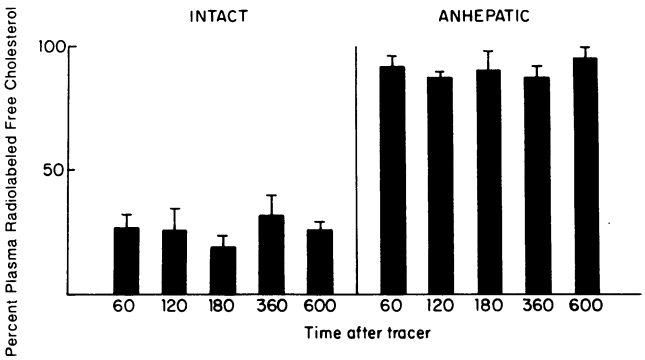

Figure 2. The recovery of radiolabeled mevalonate in plasma free and ester cholesterol in the intact and anhepatic rat (mean±SE, n = 5).

transfer to the extravascular pool ~ 10% of the control value. The anhepatic fractional removal rate (L_O) was 25% of the control. This rate may not reflect irreversible removal but rather transfer to a slowly turning over pool not reflected in the plasma decay data evaluated over the 3-h interval.

After hepatic removal with maintenance of splanchnic function a decrease in plasma cholesterol was noted. This could not be attributed to increasing plasma volumes since initial volumes (16±6 ml; n = 5) (determined by ^{125}I bovine serum albumin distribution) and volumes after 6 h (19±4 ml; n = 5) were not significantly different. Plasma albumin concentrations and hematocrit were unchanged over the first postoperative day, while a gradual decrease in plasma cholesterol occurred. In the 5 h after hepatectomy, significant decreases in both HDL (d = 1.063–1.21) and LDL (d < 1.063) (Table II) cholesterol were observed. The phospholipid contents of these anhepatic lipoproteins were also significantly less after 5 h. The free and ester cholesterol partitions were similar for respective lipoproteins in the intact and anhepatic states. The apolipoproteins of both lipoproteins were less, but this was significant only for LDL.

The mass transfer for the two compartment system (Fig. 6) was calculated from (*a*) the lipoprotein cholesterol ester contents (Table II) of intact and anhepatic rats obtained 5 h after hepatectomy, (*b*) the kinetic parameters obtained from the radiolabeled data (Table I) determined at 2–5 h after hepatectomy. Although steady-state conditions pertained for the controls, this was not true for anhepatic rats. Estimates of the sizes of the extravascular pool and of mass return to plasma from this pool in the anhepatic state are minimum values if the fall in plasma lipoprotein ester is followed by the fall in extravascular ester, and maximum if preceded by the fall in extravascular ester. We have no data to determine which condition exists. The mass estimates for both lipoproteins are, therefore, most useful in comparisons between the two, but are not absolute values of either. The flux of LDL cholesteryl ester (μg/min) between the vascular and the extravascular compartment decreased to < 10% of that seen in the intact rat. A decrease was also observed for the mass of the extravascular compartment to which the LDL cholesterol ester was transferred. It was 5% of the mass of the extravascular compartment in the intact rat. The flux of Al-HDL cholesterol ester to an extravascular compartment was less affected by the hepatectomy than was the flux of LDL cholesterol ester. About one third of the intact

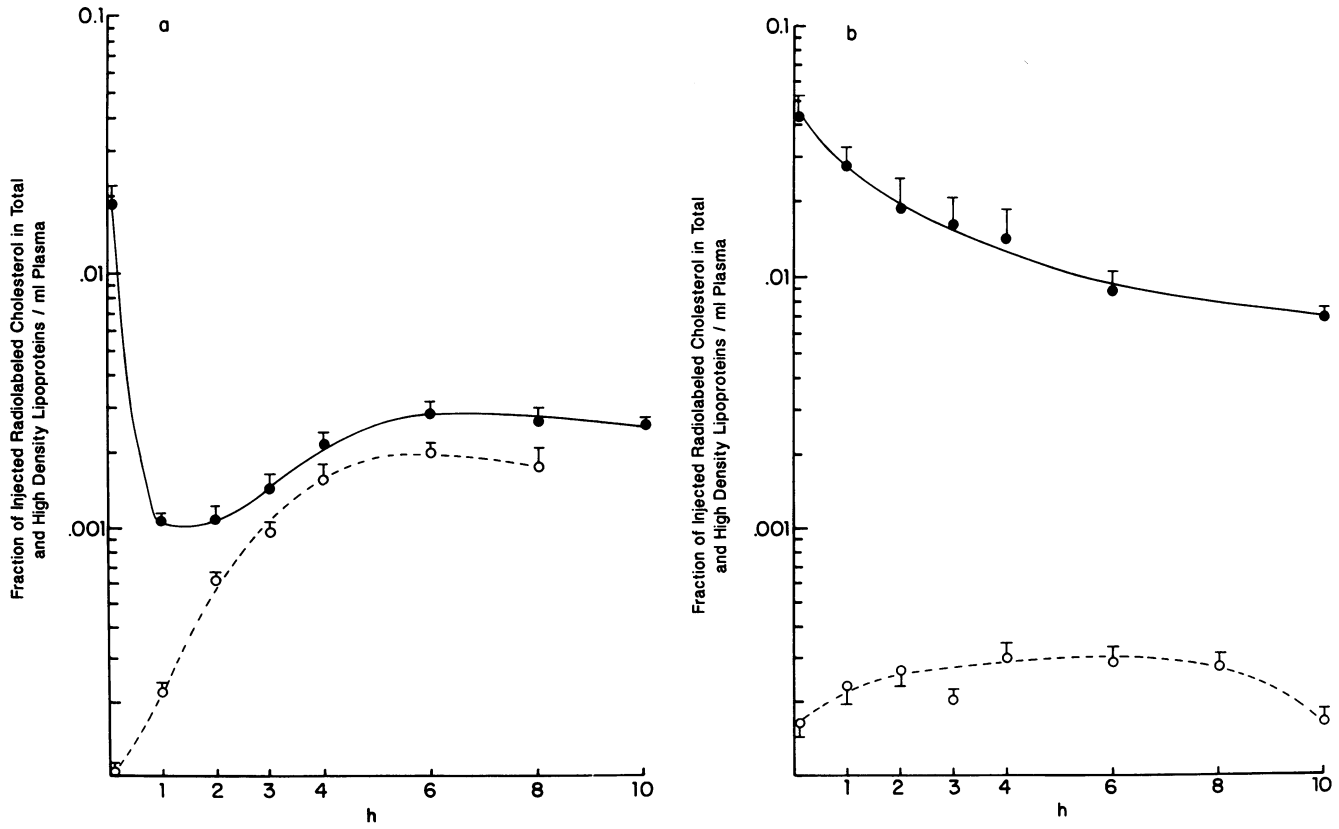

Figure 3. The fractional recovery of cholesterol in total plasma (●) and HDL (○) after the injection of chylomicron (2 mg triglyceride) [4-^{14}C]-cholesterol (79±9% ester, n = 4) in (*a*) intact and (*b*) anhepatic rats. The data represents five rats±SE for each group.

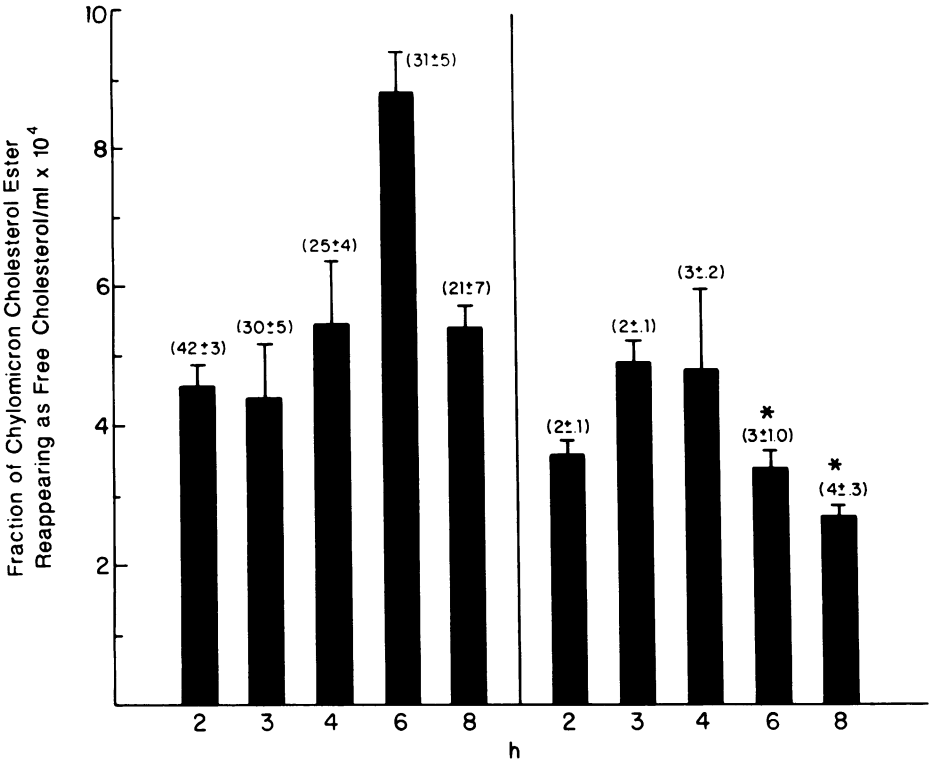

Figure 4. The fractional recovery of chylomicron [^{14}C]cholesterol ester as free cholesterol at sequential times after chylomicron injection in (*left*) intact and (*right*) anhepatic rats. The figures within the parentheses are the percent free cholesterol at each time±SE, n = 4.

Al-HDL cholesterol ester flux between plasma and extravascular pools was seen in the anhepatic state and nearly 50% of the mass remained in the extravascular pool after hepatectomy. Both the flux and the mass of extravascular Al-HDL cholesterol ester were proportionately much greater than what remained for comparable anhepatic LDL cholesterol ester transfer. The mass transfer to a more slowly turning over extravascular pool or out of the system decreased more for LDL than HDL cholesterol ester after hepatectomy.

The decay of ^{125}I apo E, added to 1 ml of plasma from standard laboratory diet-fed rats and injected into the renal artery, was appreciably more rapid in the intact than the anhepatic rat (Fig. 7 *a*). Apo ^{125}I Al, also added to plasma before

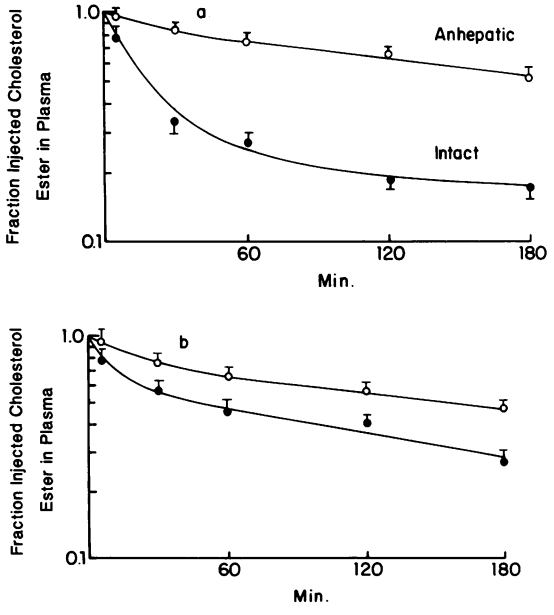

Figure 5. (*a*) The plasma decay of ^{3}H (0.15 μCi) LDL (d = 1.006–1.063) cholesterol ester (< 0.3 mg; 86% ester, n = 5) in the intact and anhepatic rat. The data represent the mean±SE of five rats in each group. (*b*) The plasma decay of ^{3}H (0.2 μCi) Al-HDL (d = 1.063–1.21) lipoprotein cholesterol ester (<0.4 mg; 89±8% ester, n = 4) in intact (•) and anhepatic (○) rats. The data represents sequential means±SE of four rats in each group. The plasma volume was determined from ^{125}I-bovine serum albumin injections (0.02 μCi) before each lipoprotein assay.

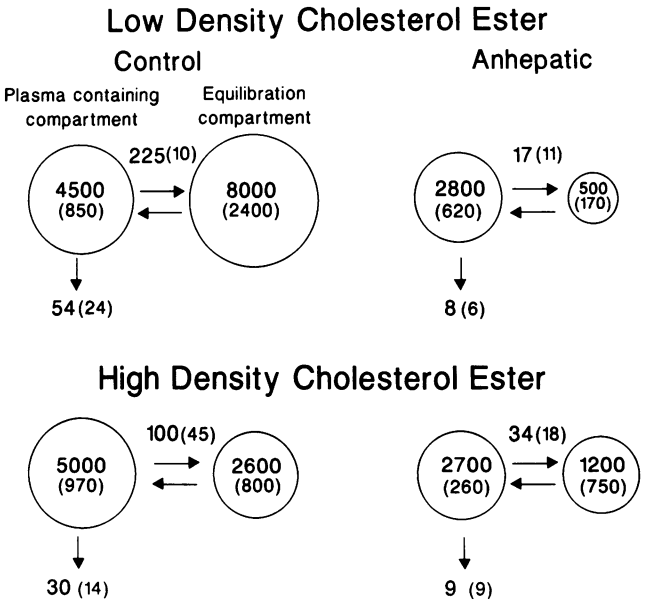

Figure 6. The pool size (*within circles*, μg±SD [within parentheses], n = 5) and fluxes (μg/min±SD, n = 4, *above and below arrows*) for control and anhepatic rats after the arterial injection of respective lipoproteins. The described mass (Table II) and tracer (Table I) data were used for these calculations.

Table I. Kinetic Parameters of Plasma HDL and LDL Cholesterol Ester in Chow-Fed Control and Anhepatic Rats

	L_E	L_P	L_O
		min^{-1}	
HDL cholesterol ester			
Control (4)	0.020±0.007	0.038±0.01	0.006±0.002
Anhepatic (4)	0.013±0.007	0.030±0.008	0.003±0.002
LDL cholesterol ester			
Control (5)	0.050±0.007	0.028±0.005	0.012±0.002
Anhepatic (5)	0.006±0.001*	0.033±0.011	0.0029±0.0008‡

The results are the means of the number of determinations indicated within parentheses. The L_E is the fractional transfer min^{-1} of plasma lipoprotein cholesterol to an equilibrating pool. L_P represents the fractional return from the equilibrating pool back to the respective plasma lipoprotein. L_0 is the fractional rate of loss from the plasma pool or transfer to a slow turning over pool. The anhepatic value is significantly less than control at ‡ $P < 0.01$ and * $P < 0.001$. Studies were begun in the anhepatic and sham-operated rats 2 h after surgery.

arterial injection, was cleared from plasma similarly (Fig. 7 *b*) in anhepatic and control rats. The kinetic analyses of the apo A1 data, employing a two-compartment model, revealed no significant differences between control and anhepatic rats (Table III). This differed from apo E, where the anhepatic fractional loss or transfer to a slower pool (L_O) was significantly less than that for the intact rat. Despite this appreciable decrease in the fractional rate of loss of apo E in the anhepatic rat and the lack of such change for apo A1, the mass of plasma apo E declined substantially after hepatectomy (Fig. 8) while that of apo A1 was better maintained. It was consistently observed (Fig. 8) that apo E in HDL (d 1.063–1.21) was lost before Apo E in LDL ($d < 1.063$).

Discussion

As previously described (21), radiolabeled mevalonate appeared promptly in the plasma cholesterol of intact rats after parenteral administration. Even though considerable newly synthetic free cholesterol was recovered in anhepatic peripheral

Table II. Plasma Lipoprotein Concentrations 5 h after Complete Hepatectomy

	Control	Anhepatic
	$\mu g/ml$	
HDL (1.063–1.21)		
Protein	315±35	259±39
Cholesterol (% Free)	227±40 (28±11)	120±12 (24±14)*
Phospholipid	466±64	254±26*
LDL (1.006–1.063)		
Protein	154±14	83±12§
Cholesterol	205±31 (30±9)	108±22 (34±12)‡
Phospholipid	247±36	121±19‡
Triglyceride	763±99	171±85§

The data are means (±SE) of eight control and eight anhepatic lab diet-fed rats evaluated after an overnight fast and 5 h after hepatectomy or sham operation. The anhepatic results are significantly different than control at * $P < 0.05$, ‡ $P < 0.02$, or § $P < 0.01$.

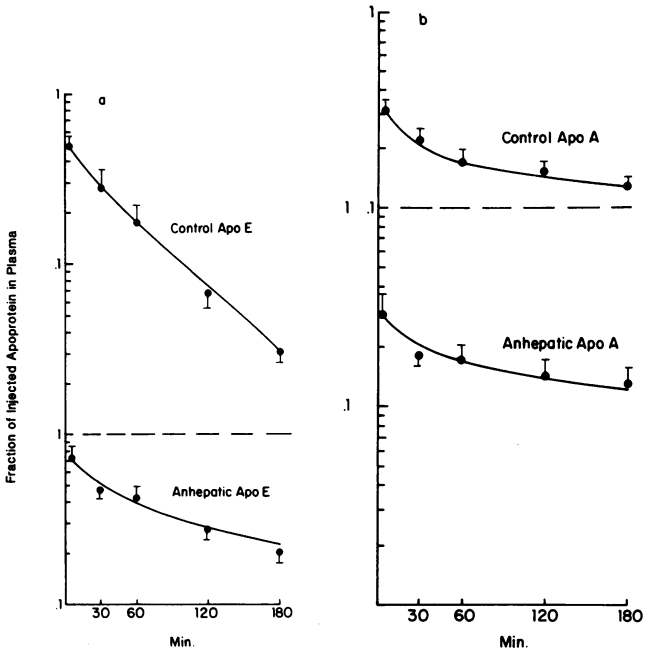

Figure 7. (*a*) The plasma apo E decay in intact (*top panel*) and anhepatic rats (*bottom panel*). The data are the means±SE for five rats in each group injected with 0.35 μCi of ^{125}I-Apo E (< 0.5 mg). (*b*) The plasma apo A1 decay in intact (*top panel*) and anhepatic rats (*bottom panel*). The data are the means±SE for four rats in each group injected with 0.5 μCi of ^{125}I apo A_1 (< 0.3 μCi). Plasma volumes were determined before each apoprotein assay by injection of 0.02 μCi bovine serum albumin.

tissue (data not shown), confirming the known cholesterol synthetic capacity of peripheral tissue (22), the contribution of this sterol to plasma cholesterol was modest. The anhepatic rat had ~10% of the plasma tracer cholesterol observed for the intact rat after tracer mevalonate. Virtually all of the mevalonate incorporated into anhepatic plasma cholesterol was in free cholesterol in contrast to the intact, where it was found mainly in cholesterol ester. The tracer recoveries in HDL free cholesterol were similar for the anhepatic and intact rats, suggesting that peripheral tissue is an important source of the free cholesterol in this lipoprotein. Only a small amount of synthetic cholesterol was isolated in LDL in the absence of the liver despite known exchange (23) of free cholesterol between the lipoproteins.

The appearance of labeled, newly synthesized free cholesterol in HDL from peripheral tissues may not indicate mass transfer to the lipoprotein but simply exchange. HDL free cholesterol readily exchanges with the free cholesterol of tissues (23, 24). Hepatic free cholesterol exchanges with this HDL pool even more rapidly than does cholesterol from red cells (24). The same mechanism responsible for this exchange may produce mass redistribution between tissues and plasma, or vice-versa, if part of the exchanging pool is sequestered (i.e., esterification, hydroxylation, etc.). This equilibrating cholesterol pool between tissues and plasma provides a mechanism for tissue cholesterol transfer which is rapid and relatively independent of the receptor activity that governs the rate of plasma particulate lipoprotein transport.

The return of enteral cholesterol to the plasma after chylomicron clearance also occurs in the HDL free cholesterol pool. This return of enteral cholesterol was coincident with an incre-

Table III. Apo E and Al Plasma Transport in Anhepatic and Laboratory Diet-Fed Rats

	L_E	L_P	L_O
		min^{-1}	
Apo Al (4)			
Control	0.042±0.018	0.049±0.021	0.0044±0.0014
Anhepatic	0.025±0.016	0.030±0.010	0.0038±0.0005
Apo E (5)			
Control	0.020±0.014	0.063±0.033	0.021±0.003
Anhepatic	0.027±0.016	0.077±0.04	0.0091±0.002*

The results are the means±SE of the number of determinations indicated in the parenthesis. The anhepatic value is significantly different than the respective control at * $P < .02$. Determinations were begun 2 h after either hepatectomy or sham surgery. The L_E, L_P and L_O indicate the same fractional rate constants as in Table I for the respective apolipoproteins.

ment in radiolabeled free cholesterol in plasma and occurred at the same time described (25) for the hepatic hydrolysis of chylomicron cholesterol ester and the loss of this sterol from liver. The anhepatic data indicates that nearly all of this returning cholesterol came from the liver and possibly entered the plasma by exchange with the HDL free cholesterol pool. The return to plasma of cleared chylomicron cholesterol and the entry of peripheral tissue newly synthesized cholesterol to the HDL free cholesterol pool demonstrates the importance of this pool in the distribution of cholesterol between tissues of standard laboratory diet-fed rats. Most tissue cholesterol in such rats is free cholesterol and is in equilibrium with the HDL free cholesterol pool. The fact that the only two inputs (i.e., enteral, synthetic) of mammalian cholesterol first appear in this plasma pool indicates the importance of this exchanging system to cholesterol homeostasis in the chow fed rat.

A previous study (7) of lipoprotein changes in the anhepatic rat described a prompt decrease in triglyceride-rich lipoproteins and an increment in apo E-rich HDL at 1 h. The only plasma lipid increase noted in longer-term anhepatic studies (8, 26) was a transient increase in plasma free fatty acid particularly after large plasma triglyceride infusions. All other plasma lipids and apolipoproteins decreased following hepatic removal. Decreases in both lower density ($d < 1.063$) and high density lipoproteins ($d = 1.063$–1.21) were consistently observed at all time intervals after hepatectomy. This progressive fall in plasma lipoprotein lipid and apoprotein concentration in the anhepatic rat was not the result of either expansion of plasma volume, or, according to the kinetic determinations, a redistribution of the plasma lipoproteins to the extravascular space. Despite the decreased outflow of cholesterol ester or apo E after hepatectomy, the only plausible reason for the falling plasma concentration of both is a plasma input even less than the outflow.

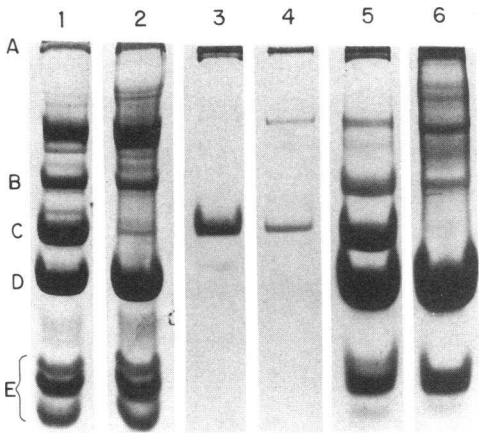

Figure 8. The SDS-PAGE of representative total lipoproteins in intact (lane *1*) and anhepatic rats (lane *2*) 5 h after hepatectomy. The apolipoproteins of LDL ($d < 1.063$) of intact (lane *3*) and anhepatic (lane *4*) and those of HDL ($d = 1.063$–1.21) in intact (lane *5*) and anhepatic rats (lane *6*). Band A, apo B; band B, apo AIV; band C, apo E; band D, apo AI; band E, apo C.

The rate of fall of anhepatic plasma cholesterol is considerably greater than the turnover rate of cholesterol in the laboratory diet-fed rat (27). This indicates that this effect of hepatectomy is in addition to the major role which the liver plays in cholesterol anabolism and catabolism. The kinetic studies of cholesterol ester indicate that hepatectomy considerably contracts the extravascular pools with which both A1-HDL and LDL cholesterol ester exchanges. This is particularly pronounced for the low density ester, where virtually the entire equilibrating pool was lost after hepatectomy. This equilibrating hepatic pool may function as a reservoir to buffer plasma lipoprotein concentrations. Data from immunolocalization studies of both apo B and apo E in the rat liver has documented (28, 29) considerable amounts of both in the extracellular (sinusoidal, Disse) space. It was not determined which lipids were associated with these apoproteins, but these data and the results described here suggest this extracellular space may well be the hepatic site of the buffering lipoproteins. It is likely that the impressive changes in the plasma decay of both LDL cholesterol ester and apo E after hepatectomy were due to the removal of the extracellular stores of these apolipoproteins and/or lipoproteins. The speculation that these extracellular hepatic stores serve as reservoirs to buffer plasma lipoprotein changes was proposed because of the appreciable lipoprotein concentration decreases after hepatectomy and will require in vivo confirmation. The depletion of plasma albumin produces a transfer of extravascular albumin into the plasma to buffer this loss (30). It is possible that a similar system occurs with lipoproteins and is fed by an extracellular hepatic pool. This pool, in the space of Disse, would also be continuously influenced by enzymes within this space and by the endosomal processing to which such a pool would be exposed. These influences would suggest that considerable lipoprotein interconversion would occur in such a pool.

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