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Rates of receptor-dependent and -independent low density lipoprotein uptake in the hamster

(cholesterol synthesis/liver/methylated low density lipoprotein/low density lipoprotein turnover)

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ABSTRACT **By using a constant infusion technique in the hamster, rates of uptake of [^{14}C]sucrose-labeled hamster low density lipoprotein (hamLDL) and methylated hamster LDL (Me-hamLDL) were directly measured in 15 tissues. From these measurements the magnitude of LDL receptor-dependent and receptor-independent lipoprotein transport was calculated. The whole-animal clearance of hamLDL equaled 547 μl/hr per 100 g of body weight. LDL clearance per g of tissue was highest in the liver (114 μl/hr per g), ovary (43), spleen (36), adrenal gland (29), and intestine (24) and was lowest in fat (0.75), brain (0.35), and muscle (0.26). When adjusted for organ weight, the sum of the absolute clearance rates in all of the tissues examined equaled the rate of whole-animal LDL turnover. Liver accounted for 73%, and the jejunum and ileum combined accounted for 7% of whole-animal clearance. The 12 other tissues each accounted for only a minor portion of LDL clearance. Rates of uptake of Me-hamLDL were much less in many tissues and accounted for only 6–12% of the uptake of LDL in the liver, ovary, adrenal gland, lung, and kidney. However, this receptor-independent uptake was quantitatively more important in the intestine (44%) and spleen (72%) and accounted for essentially all LDL uptake in organs such as muscle, skin, and brain. Thus, in the hamster, most LDL is taken up and degraded by the liver. This uptake process is >90% mediated by the LDL receptor and manifests saturation kinetics. Finally, cholestyramine feeding increases receptor-mediated LDL transport in the liver but in no other tissue studied.**

One critical determinant of the low density lipoprotein (LDL) concentration in plasma is the rate at which LDL is taken up and degraded by various organs. This uptake process involves at least two separate mechanisms, which have been termed receptor-dependent and receptor-independent transport. Receptor-dependent transport is a saturable process that involves binding of LDL molecules to specific receptors on the cell surface, followed by internalization and degradation (1, 2). Receptor-independent transport is poorly characterized but is probably a nonsaturable process (or processes) whereby LDL also is taken into cells and degraded. Receptor-independent clearance has generally been studied in isolated cells and in whole animals by measuring rates of uptake and degradation of LDL that has been modified chemically to block its interaction with the LDL receptor (3–5). Such studies indicate that in all species so far examined, the receptor-dependent and -independent mechanisms are both quantitatively important in determining rates of whole-animal LDL cholesterol turnover (5–8).

However, there is little information available on the actual rates of receptor-dependent and -independent LDL transport into specific organs under varying physiological circumstances. The data that are available have been derived largely by using techniques that only indirectly reflect the rates of transmembrane LDL movement, such as measurement of LDL binding to cell membranes (9), quantitation of the tissue accumulation of a poorly metabolized marker conjugated to LDL (10), delineation of the effect of organ removal on whole-animal LDL turnover (8), and measurement of rates of LDL degradation by isolated perfused organs (11). Furthermore, the quantitative significance of many of these studies has been limited by the use of heterologous LDL, which is usually neither bound nor taken up at rates equivalent to those of the homologous LDL (8, 12).

In the current studies, rates of transport of homologous LDL and methylated LDL were measured directly in 15 tissues of the hamster by a constant infusion technique. These measurements were made under conditions where the plasma LDL concentration was normal or elevated and where the rates of sterol synthesis in the liver were altered. These data demonstrate that the liver is the major site for LDL removal from the plasma and that >90% of this uptake is through a regulable and saturable receptor-mediated process.

METHODS

Animals. Most studies were performed with Golden Syrian female hamsters (Charles River Lakeview, Newfield, NJ) weighing 100–130 g that were subjected to light cycling and fed a low-cholesterol diet (Wayne Lab Blox, Allied Mills, Chicago) for at least 2 wk before use (13). In one study on the kinetics of LDL transport, similarly treated male hamsters were used because the rate of LDL uptake into the adrenal gland is higher in this sex. In another study, female hamsters were fed either the ground chow diet alone or ground chow diet to which cholestyramine (2 g/100 g of diet) had been added for 1 wk before they were used.

Lipoprotein and Albumin Preparations. Hamster LDL (hamLDL) was isolated at density 1.020–1.055 g/ml from the plasma of donor animals fed a low-cholesterol diet. This preparation showed only B apoprotein on polyacrylamide gels. Hamster serum albumin was used as supplied (Research Plus, Bayonne, NJ). The hamLDL was labeled with either ^{125}I (14) or [^{14}C]sucrose (10), and a portion then was reductively methylated (Me-hamLDL; 80–87% in different batches) (3); hamster serum albumin also was conjugated to [^{14}C]sucrose. The lipoprotein fractions and albumin were then dialyzed against 0.9% NaCl solution, passed through a 0.45-μm Millipore filter, and used in experiments within 12 hr.

Whole-Animal Lipoprotein Clearance Rates. The turnover of hamLDL in the whole animal was performed as described

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Abbreviations: LDL, low density lipoprotein; hamLDL, LDL derived from hamster plasma; Me-hamLDL, methylated hamLDL; VLDL, very low density lipoprotein.

(8, 15). Each animal was fitted with a femoral vein catheter, and the LDL was infused at a constant rate for 14–16 hr. The rate of infusion of radiolabeled LDL (dpm/hr) divided by the steady-state plasma radiolabeled-LDL concentration (dpm/μl) gave the plasma clearance rate expressed as μl of plasma cleared of its LDL content per hr. This value was then normalized to 100 g of body weight to give whole-animal plasma LDL clearance rates in units of μl/hr per 100 g.

Determination of Tissue Lipoprotein Uptake (Clearance) Rates. The experimental animals were fitted with femoral vein catheters and placed in restraining cages. Each animal was then given a tracer dose of a radiolabeled protein as a bolus over 1–2 min, followed by a constant infusion of the same molecule for 6 hr (Fig. 1). By using the measured plasma clearance rates of the lipoprotein preparations, the amount of radioactivity infused per hr was adjusted relative to the dose given as a bolus to maintain the specific activity of the radiolabeled protein constant in the plasma during the 6-hr experiment (Fig. 1*B*). Groups of four animals were then killed at 10 min, 2 hr, 4 hr, and 6 hr, and 15 different tissues were quickly removed. Aliquots of these organs, along with plasma samples, were saponified, neutralized, solubilized, and assayed for radioactivity (with quench correction) as described (15). The tissue spaces achieved by each radiolabeled protein were calculated by dividing the radioactivity in 1 g of each organ (dpm/g) by the steady-state concentration of radioactivity in the plasma (dpm/μl); thus, the space of distribution achieved at each time point by the LDL preparations and albumin had the units μl/g (Fig. 1*A*).

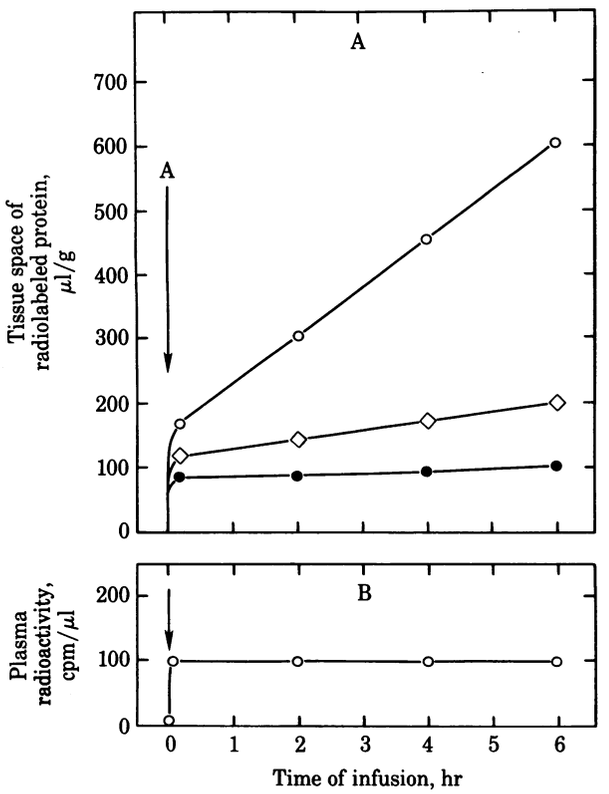

FIG. 1. Experimental protocol for the measurement of [^{14}C]sucrose-labeled protein uptake in different organs of the hamster. (*A*) At time 0 a tracer dose of radiolabeled protein is administered intravenously over 1–2 min, followed by commencement (arrow A) of continuous infusion of sufficient amounts of the same [^{14}C]sucrose-labeled protein to maintain a constant specific activity of the protein in the plasma (see *B*). In different groups of animals (16 hamsters in each group), such experiments were carried out with [^{14}C]sucrose-hamLDL (○), [^{14}C]sucrose-Me-hamLDL (◇), and [^{14}C]sucrose-labeled hamster serum albumin (●). Four animals from each group were killed at 10 min, 2 hr, 4 hr, and 6 hr, and 15 different tissues were removed. The radioactivity present in 1 g of each organ was assayed (dpm/g), and this value was divided by the concentration of the radiolabeled protein in the plasma (dpm/μl). This calculation yields the tissue space of distribution achieved by each radiolabeled compound in a particular organ at each time interval (*A*). The slope of the linear regression curves gives the rate of tissue uptake of the various test molecules expressed as the microliters of plasma cleared of hamLDL or albumin content per hr by 1 g of tissue.

In a preliminary experiment, 28 hamsters were given [^{14}C]-sucrose-labeled hamLDL ([^{14}C]sucrose-hamLDL), and groups of 6 animals were killed every 24 hr for 4 days. From these data the rates of loss of ^{14}C from each organ per 6-hr interval could be determined and were as follows: small bowel, 8%; liver, 4%; ovary, 3%; colon and spleen, 2%; adrenal gland, 1.3%; and all other tissues, <1%. Because these losses were small compared to the rates of uptake of hamLDL and because the concentration of the radiolabeled protein was constant during the 6-hr experimental period, the radiolabeled proteins should accumulate in each organ as a linear function of the time of infusion (Fig. 1*A*). The slope of this relationship equaled the rate of protein movement into each organ and was expressed as the μl of plasma cleared of hamLDL or albumin per hr per g of tissue (μl/hr per g). When multiplied by the weight of a particular tissue, these values yielded an absolute rate of clearance into the whole organ (μl/hr per organ). Finally, when either of these clearance values was multiplied by the concentration of LDL-cholesterol in 1.0 μl of plasma, the absolute rate of LDL-cholesterol uptake per g of tissue or per organ was obtained.

Calculations. Mean values ± 1 SEM are given. The clearance rates of the various lipoproteins and albumin (Fig. 2 and Table 1) were calculated by fitting the data points obtained in each organ in 16 animals to the best-fit linear regression curve, the slope of which equaled the rate constant for the uptake of that protein in that particular organ (Fig. 1*A*).

RESULTS

Initial experiments were performed to determine if the rate of whole animal turnover of hamLDL was the same when the lipoprotein was labeled with [^{14}C]sucrose as when it was labeled with ^{125}I. Beginning with a single batch of hamLDL, both the ^{125}I- and [^{14}C]sucrose-labeled fractions were prepared, and whole-animal clearance rates were measured simultaneously in groups of six animals with each isotopically labeled preparation. In this study whole-animal clearance equaled 613 ± 12 μl/hr per 100 g of body weight with ^{125}I-labeled hamLDL and 611 ± 19 μl/hr per 100 g with [^{14}C]sucrose-hamLDL.

Because the hamLDL preparations labeled with [^{14}C]sucrose gave turnover rates that were nearly identical to those labeled with ^{125}I and because only a small amount of the ^{14}C was lost from tissues as a function of time, it was evident that [^{14}C]sucrose-labeled lipoproteins could be utilized to measure rates of LDL uptake into the various tissues of the hamster as has been demonstrated previously in the rat (16). As shown by the representative data in Fig. 2, there was a linear increase in the space of distribution attained by the hamLDL in all organs, although the rate of LDL uptake varied markedly among these organs. When expressed per g of tissue, the highest rates of hamLDL uptake were found in the liver, ovary, spleen, and adrenal gland, which cleared 114, 43, 36, and 29 μl of plasma of its LDL content per hr, respectively (Table 1, column 2). The lowest rates of uptake were found in fat, brain, and skeletal muscle, all of which cleared <1 μl/hr per g of plasma hamLDL. To determine losses of isotope into bile and urine, a separate group of animals was fitted the same day with catheters in both the common bile duct and urinary bladder; the rate of clearance

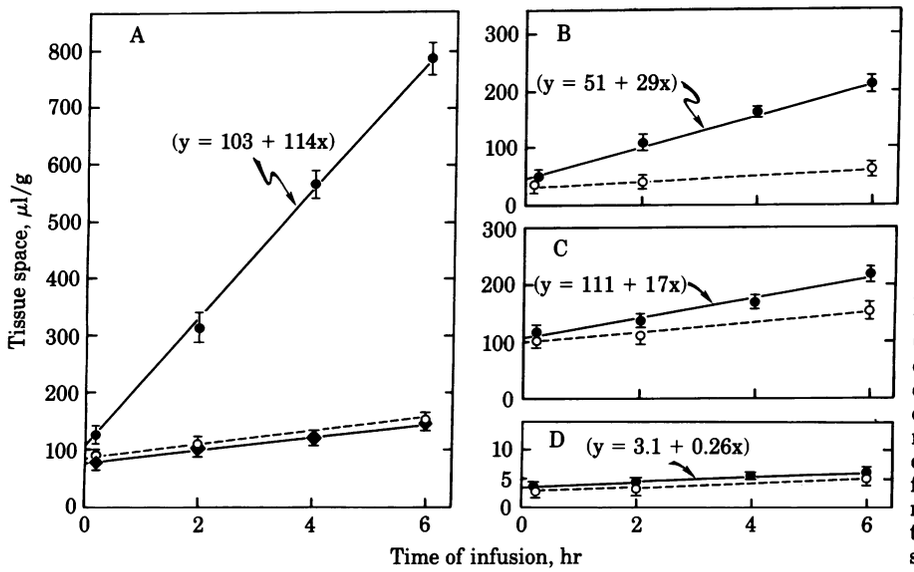

FIG. 2. Representative experimental data for the uptake of hamLDL (●), Me-hamLDL (○), and hamster serum albumin (◆)—all labeled with [^{14}C]sucrose—by liver (*A*), adrenal gland (*B*), lung (*C*), and skeletal muscle (*D*). Groups of hamsters were infused and the rates of tissue clearance were determined as in Fig. 1. In the case of the adrenal gland, lung, and skeletal muscle, the curves for albumin are omitted because they were superimposable upon the curves for Me-hamLDL. Each point represents the mean ± 1 SEM for four animals. The slope of the linear regression line giving the rate of tissue uptake of hamLDL is shown.

of ^{14}C into bile and urine equaled 59 and 7 μl/hr per g, respectively.

When these rates were multiplied by the respective organ weights (Table 1, column 1), the absolute rates of hamLDL uptake by each tissue were obtained (Table 1, column 3). The liver was by far the most important organ, clearing 401.3 μl of plasma of its hamLDL content per hr per 100 g of body weight. The small intestine (37.6 μl/hr per 100 g) and spleen (21.6 μl/hr per 100 g) also cleared significant but much smaller amounts. With the same batch of hamLDL, whole-animal turnover rates were measured in a separate group of six animals on the same day and were found to equal 547 ± 19 μl/hr per 100 g of body weight. Because the sum of the clearance rates found in the individual organs (Table 1, column 3) equaled 537 μl/hr per 100 g of body weight, it is apparent that in these studies essentially 100% of whole-animal turnover could be accounted for by the sum of the clearance rates found in each of the 15 organs plus the small amounts of ^{14}C found in bile and urine. Thus, the percentage contribution of each tissue to whole-animal turnover could be accurately calculated and is shown in Table 1, column 4. In this species 73% of the turnover of LDL was accounted for by hepatic uptake, whereas 6.6% occurred in the small bowel. The remaining organs played only a minimal role in the degradation of hamLDL and, in particular, the largest organ, skeletal muscle, cleared only 2.1% of the plasma LDL.

Methylation of hamLDL had a variable effect upon the rate of lipoprotein clearance by the various organs (Fig. 2). In liver, for example, [^{14}C]sucrose-labeled Me-hamLDL ([^{14}C]sucrose-

Table 1. Rates of [^{14}C]sucrose-hamLDL clearance by the individual tissues of female hamsters under control conditions

Tissue	Tissue weight, g/100-g animal*	[^{14}C]Sucrose-hamLDL clearance: Tissue,† μl/hr per g of tissue	[^{14}C]Sucrose-hamLDL clearance: Organ, μl/hr per 100-g animal	Percentage of the whole-animal clearance rate‡
Liver	3.52	114.0 ± 1.9	401.3	73.0
Ovary	0.03	43.0 ± 3.4	1.3	0.2
Spleen	0.60	36.0 ± 0.75	21.6	3.8
Adrenal	0.02	29.0 ± 0.75	0.6	0.1
Ileum	0.80	29.0 ± 0.73	23.2	4.1
Jejunum	0.80	18.0 ± 0.45	14.4	2.5
Lung	0.50	17.0 ± 0.48	8.5	1.5
Kidney	0.76	5.8 ± 0.30	4.4	0.8
Heart	0.36	4.2 ± 0.40	1.5	0.3
Colon	0.66	3.1 ± 0.10	2.0	0.4
Stomach	0.67	2.4 ± 0.11	1.6	0.3
Skin	11.00	1.5 ± 0.08	16.5	3.0
Fat	10.00	0.75 ± 0.05	7.5	1.3
Brain	0.64	0.35 ± 0.08	0.2	<0.1
Skeletal muscle	45.00	0.26 ± 0.02	11.7	2.1
Urine	0.35	7.0 ± 1.0	2.5	1.5
Bile	0.30	59.0 ± 2.0	17.7	3.1

* The tissue weights are normalized to 100 g of body weight. The values given for urine and bile represent the grams of these two fluids produced by 100-g animals per hr.

† Mean values ± 1 SEM for data obtained from 16 animals.

‡ These values are calculated by using a whole-animal clearance rate for [^{14}C]sucrose-hamLDL equal to 547 ± 19 μl/hr per 100 g of body weight. This value was obtained in a separate group of six animals run the same day with the same batch of [^{14}C]sucrose-hamLDL with which the data in the table were derived.

Me-hamLDL) was cleared at a rate of only 7.2 ± 1.5 μl/hr per g, compared to the rate of 114 ± 1.9 μl/hr per g for hamLDL, whereas [^{14}C]sucrose-labeled hamster albumin was taken up at a rate of 10.0 ± 0.9 μl/hr per g. In contrast, in skeletal muscle [^{14}C]sucrose-Me-hamLDL and [^{14}C]sucrose-labeled albumin clearance equaled 0.25 ± 0.05 and 0.21 ± 0.02 μl/hr per g, respectively, rates which were not significantly different from the clearance of [^{14}C]sucrose-hamLDL (0.26 ± 0.02 μl/hr per g) in that organ. Thus, as summarized in Fig. 3, in tissues such as liver, ovary, adrenal gland, and kidney, the rate of clearance of [^{14}C]sucrose-Me-hamLDL equaled only 6.3–12% of the rate of uptake found with [^{14}C]sucrose-hamLDL, a result implying that, in these tissues, about 90% of LDL uptake occurred by a receptor-mediated mechanism. In contrast, in organs such as jejunum and spleen, receptor-independent LDL transport played a greater role, and, in tissues such as skeletal muscle, fat and brain, this process accounted for essentially all of the observed lipoprotein transport.

If LDL transport into tissues like liver and adrenal gland were mediated primarily by the LDL receptor, then such uptake should manifest saturability. By giving mass amounts of unlabeled hamLDL along with the bolus and constant infusion of [^{14}C]sucrose-hamLDL, the rates of LDL uptake could be measured in these organs under circumstances where the plasma LDL level had been abruptly raised and then maintained at a new constant value for 6 hr. As seen in Fig. 4*A*, when this was done in four male hamsters, the clearance of hamLDL decreased markedly in the liver (from 179 to 55 μl/hr per g) and adrenal gland (from 81 to 16 μl/hr per g) as the plasma LDL-cholesterol level was elevated from 22 to 393 mg/dl. When these clearance rates were multiplied by the respective concentrations of plasma LDL-cholesterol, the absolute rates of LDL-cholesterol uptake were obtained (Fig. 4*B*). It is evident that cholesterol uptake increased in a curvilinear fashion in both the liver (from 39 to 215 μg/hr per g) and adrenal gland (from 18 to 62 μg/hr per g), implying that the major transport process in these organs was saturable.

Finally, to determine if the rate of LDL transport is regulable in any organ in this species, female hamsters were fed cholestyramine, and hamLDL transport was measured in the various tissues. Cholestyramine treatment increased LDL uptake by the liver from the control value of 134 ± 8 to 195 ± 8 μl/hr per g. In contrast, this treatment did not influence LDL uptake in the ovaries (48 ± 2 versus 37 ± 3 μl/hr per g), adrenal glands (23 ± 2 versus 29 ± 3 μl/hr per g), kidneys (7 ± 1 versus 9 ± 2 μl/hr per g), and skeletal muscle (0.13 ± 0.11 versus 0.15 ± 0.10 μl/hr per g). Thus, enhanced bile acid turnover and hepatic cholesterol synthesis induced by cholestyramine feeding was associated with a selective increase in the rate of hepatic LDL transport.

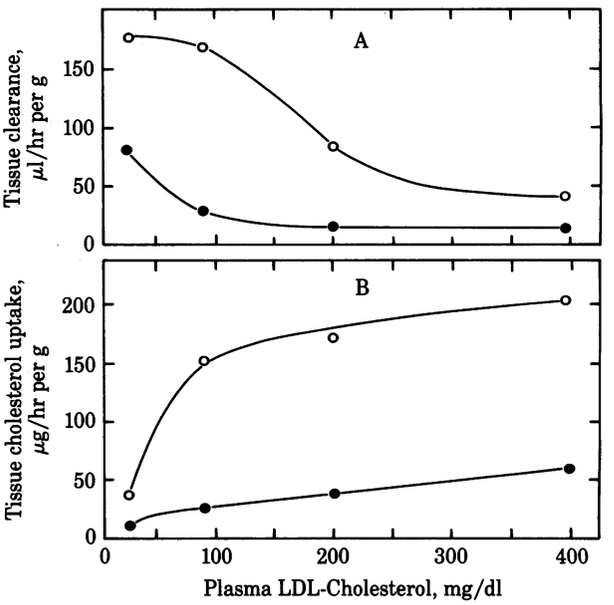

FIG. 4. Rates of hamLDL uptake in the liver (○) and adrenal gland (●) at different concentrations of hamLDL in the plasma. Male hamsters were infused with different mass amounts of hamLDL (also containing [^{14}C]sucrose-hamLDL) to abruptly achieve new steady-state levels (varying from 22 to 393 mg/dl) of circulating hamLDL-cholesterol in the plasma at time 0. (*A*) Rates of [^{14}C]sucrose-hamLDL clearance at the different plasma LDL-cholesterol concentrations. (*B*) When each of the tissue clearance rates in *A* was multiplied by the plasma concentration of LDL-cholesterol found in the same animal, the absolute rates of LDL-cholesterol uptake were obtained. Each point represents the result obtained in one animal.

DISCUSSION

In contrast to most other small experimental animals, cholesterol metabolism in the hamster more closely resembles that in man (17). For example, the rates of total body and hepatic cholesterol synthesis are relatively low in both of these species when expressed per kg of body weight and equal only about 1/10th the rates found in the rat (18). In addition, the hamster, like

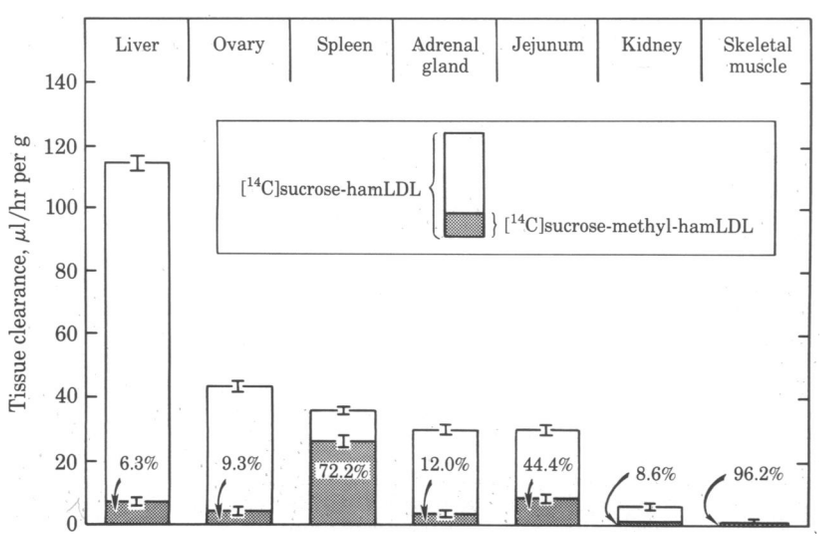

FIG. 3. Receptor-dependent and receptor-independent hamLDL uptake in various tissues. Tissue clearance rates were determined in seven organs utilizing both [^{14}C]sucrose-hamLDL and [^{14}C]sucrose-Me-hamLDL. The overall height of each bar gives the total rate of LDL clearance by each tissue, while the hatched area (and percentage figure) shows that portion attributable to receptor-independent mechanisms. The results represent the means ± 1 SEM for data obtained in 12–16 animals in each group.

man, carries much of its plasma cholesterol in LDL, responds to cholestyramine feeding with a fall in the concentration of plasma cholesterol, secretes bile relatively saturated with sterol, and develops cholesterol gallstones under certain dietary manipulations (13, 18). Finally, receptor-dependent and receptor-independent mechanisms for the degradation of lipoproteins are important in both species for the turnover of plasma LDL.

In order to quantitate the role of each tissue in the hamster in LDL degradation, a constant infusion technique that has certain advantages over previously utilized methods was used in the present studies. The rates of transport were measured over relatively short periods of time in order to minimize artifacts due to differences in rates of loss of ^{14}C from the various organs. Furthermore, these rates were measured as a time-dependent slope and so were independent of the marked differences that exist in the background spaces of distribution of the radiolabeled LDL in the vascular and extravascular compartments of the different organs. Finally, and of particular importance, the sum of the clearance rates observed in all of the tissues quantitatively accounted for the rate at which LDL was removed and degraded from the plasma compartment of the whole animal.

From these studies, it is clear that the hamster liver takes up 3 to 5 times more LDL per g of tissue than the next most active group of organs, which includes the ovary, spleen, adrenal gland, small bowel, lung, and kidney. It is noteworthy that in the rat this same group of organs responds to a lowering of the plasma cholesterol level with enhanced rates of cholesterol synthesis (19). Thus, these particular tissues apparently do derive a portion of their daily needs for cholesterol from the uptake of LDL and, in the absence of such uptake, will increase the rate at which they synthesize sterol. In contrast, most of the remaining organs of the body, including such large tissues as skin, central nervous system, and striated muscle, take up very little LDL and, as a correlate of this, do not alter their rates of sterol synthesis when deprived of this source of cholesterol (19). Such tissues presumably derive most of the sterol they require from local synthesis.

These studies also demonstrate that the high rate of LDL clearance observed in liver, ovaries, adrenal gland, lung, and kidney is achieved primarily through receptor-dependent uptake, which accounts for ≈90% of the LDL transport found in this group of organs. Receptor-independent LDL transport is relatively more important in achieving the high rates of LDL uptake also seen in the intestine and spleen, possibly reflecting the large numbers of phagocytic cells present in the splenic pulp and in the villus core of the intestine. In the remaining organs there is no evidence for receptor-mediated LDL transport because the rate of uptake of hamLDL was no greater than the rates of uptake for ME-hamLDL and hamster serum albumin.

Because of both the high rate of receptor-mediated transport per g of tissue and the large organ size, the liver is the major site for the removal of plasma LDL, accounting for 73% of the degradation that takes place. In this species, and probably also in man (17, 18), the liver has a relatively low rate of cholesterol synthesis, whereas the extrahepatic tissues have high rates and may synthesize most of the sterol they require to meet metabolic needs. Hence, in the hamster most of the apoprotein B that is secreted from the liver in very low density lipoproteins (VLDL) is returned to the liver carried either in VLDL remnants or in LDL. Relatively little is delivered to the peripheral organs.

Whether or not the liver plays such an important role in other species remains to be determined. Utilizing this same technique in the rat, we have found that the liver accounts for the degradation of only 52% of plasma LDL, but this species is anomalous in that the liver is a major contributor to total body cholesterol synthesis (17). In the only other species that has been studied with purified homologous LDL, the liver was reported to account for 39% of LDL degradation in the pig (10). It is also not known whether hepatic LDL uptake in other species is nearly all receptor-mediated and, therefore, potentially regulable as it is in the hamster; however, it has been demonstrated that combined treatment with cholestyramine and mevinolin in the dog markedly increases LDL binding to liver cell membranes and is associated with more rapid LDL turnover (20). In any event, if future experiments demonstrate that one of the major mechanisms for LDL degradation in most species is receptor-mediated uptake by the liver, then it will be important to understand how this process is affected by such factors as aging, quantitative and qualitative changes in the enterohepatic circulation of bile acids, and the administration of various drugs.

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