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Dietary saturated triacylglycerols suppress hepatic low density lipoprotein receptor activity in the hamster

(cholesterol synthesis/cholesteryl esters/liver/polyunsaturated triacylglycerols)

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ABSTRACT **The liver plays a key role in the regulation of circulating levels of low density lipoproteins (LDL) because it is both the site for the production of and the major organ for the degradation of this class of lipoproteins. In this study, the effects of feeding polyunsaturated or saturated triacylglycerols on receptor-dependent and receptor-independent hepatic LDL uptake were measured *in vivo* in the hamster. In control animals, receptor-dependent LDL transport manifested an apparent K_m value of 85 mg/dl (plasma LDL–cholesterol concentration) and reached a maximum transport velocity of 131 μg of LDL–cholesterol/hr per g, whereas receptor-independent uptake increased as a linear function of plasma LDL levels. Thus, at normal plasma LDL–cholesterol concentrations, the hepatic clearance rate of LDL equaled 120 and 9 μl/hr per g by receptor-dependent and receptor-independent mechanisms, respectively. As the plasma LDL–cholesterol was increased, the receptor-dependent (but not the receptor-independent) component declined. When cholesterol (0.12%) alone or in combination with polyunsaturated triacylglycerols was fed for 30 days, receptor-dependent clearance was reduced to 36–42 μl/hr per g, whereas feeding of cholesterol plus saturated triacylglycerols essentially abolished receptor-dependent LDL uptake (5 μl/hr per g). When compared to the appropriate kinetic curves, these findings indicated that receptor-mediated LDL transport was suppressed ≈30% by cholesterol feeding alone and this was unaffected by the addition of polyunsaturated triacylglycerols to the diet. In contrast, receptor-dependent uptake was suppressed ≈90% by the intake of saturated triacylglycerols. As compared to polyunsaturated triacylglycerols, the intake of saturated lipids was also associated with significantly higher plasma LDL–cholesterol concentrations and lower levels of cholesteryl esters in the liver.**

In the steady state, the circulating level of cholesterol carried in low density lipoproteins (LDL) is determined by the rate of production of this class of lipoproteins relative to the rate at which it is removed from the circulation. In the normal hamster, rat, and rabbit and in man, 60–80% of LDL degradation apparently is mediated by LDL receptors, whereas the remainder is accomplished by receptor-independent mechanisms (1–5). Although LDL uptake can be identified in many different organs, recent studies carried out *in vivo* have shown that the liver is responsible for the uptake of 65–80% of the LDL that is cleared from the plasma in species like the hamster, rat, rabbit, and dog. Furthermore, in these same species >90% of the hepatic uptake of LDL is receptor-mediated (refs. 4, 6, and 7 and unpublished data). It is likely that the same is true in man (8). Thus, in species for which quantitative data are available, approximately 85–90% of all LDL-receptor activity demonstrable in the live animal is found in the liver. It follows from these observations that any dietary or pharmacological manipulation that alters plasma LDL levels probably does so either by changing the rate of LDL synthesis or by altering the levels of LDL receptors on the hepatocytes.

The current studies were designed to investigate whether dietary polyunsaturated and saturated triacylglycerols mediate their well-known effects on circulating LDL levels by altering either receptor-dependent or receptor-independent LDL transport in the liver. Selection of the male hamster as the animal of choice for these studies was dictated by several recent observations. Rates of cholesterol synthesis in the whole animal in species such as the rat are exceptionally high (≈120 mg/day per kg of body weight), whereas the hamster and man have much lower rates (9). Of greater importance, the rate of sterol synthesis in the liver of the hamster is disproportionately low and in the range found in biopsy specimens of human liver (9, 10). Because of this very limited synthetic capacity, the liver of man and, particularly, the male hamster cannot readily adapt to changes in cholesterol flux and so alters rates of LDL transport in response to changes in diet or to a pharmacological challenge (4, 7). Thus, hamster and man are similar in having significant levels of circulating LDL–cholesterol, in their intrinsically low rates of hepatic cholesterol synthesis, in their response to different diets and drugs, and in the manner in which they handle biliary sterol secretion (9, 11, 12). Utilizing the male hamster, then, detailed investigations were undertaken to characterize LDL transport in the liver and to examine how dietary triacylglycerols alter this transport process.

METHODS

Animals and Diets. Male Golden Syrian hamsters (Charles River Breeding Laboratories) were subjected to light/dark cycling and fed control, ground rodent diet (Allied Mills, Chicago). After 2 weeks, animals were either continued on the control diet or placed on a diet containing cholesterol (0.12%, wt/wt), cholesterol (0.12%) plus safflower oil (20%, ICN), or cholesterol (0.12%) plus hydrogenated coconut oil (20%, ICN). The iodine values of the polyunsaturated (safflower) and saturated (hydrogenated coconut oil) triacylglycerols were approximately 130 and 4, respectively. It should be noted, however, that these triacylglycerol preparations vary in chainlength, as well as in degree of saturation. Each of the diets was fed for either 3 or 30 days. All experiments were performed during the mid-dark phase of the light cycle, with animals of 100–130 g.

Lipoprotein Preparations. Hamster and human LDL was isolated from plasma by preparative ultracentrifugation in the density range 1.020–1.055 g/ml and labeled with [1-^{14}C]-sucrose (Amersham) (4, 13). The donor hamsters had been maintained on the regular, low-cholesterol diet since birth.

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Abbreviations: LDL, low density lipoproteins; methyl-hLDL, methylated human LDL.

Hamster and human LDL in this density range contained almost exclusively apoprotein B-100, as judged by electrophoresis in polyacrylamide gels. Human LDL was methylated (methyl-hLDL) (1, 14). All lipoprotein fractions were used within 24 hr of preparation and were filtered through 0.45-μm Millipore filters immediately prior to use.

Determination of the Rate of Hepatic LDL Uptake. Rates of hepatic LDL clearance were determined by use of a primed-continuous infusion of [^{14}C]sucrose-labeled LDL (4, 7). The radioactivity present in the priming dose relative to the radioactivity subsequently delivered each hour was adjusted so as to maintain a constant specific activity of the lipoprotein in plasma throughout the experimental period. Groups of six animals then were killed hourly and aliquots of plasma and liver were assayed for ^{14}C content (4, 15). The content of radioactivity in the liver at each time point was expressed in terms of the tissue space of the [^{14}C]sucrose-LDL [i.e., the volume of plasma that would contain an equivalent amount of radioactivity (4)]. The increase in this tissue space was a linear function of the time of infusion and represents the microliters of plasma cleared of its LDL content per hour per gram of liver (μl/hr per g). This clearance rate was also multiplied by the plasma LDL–cholesterol concentration to give the absolute mass of LDL–cholesterol taken up per hour by each gram of liver (μg/hr per g).

Determination of Sterol Synthesis Rates *in Vivo*. As previously described (16, 17), animals were administered [^{3}H]water (≈50 mCi; 1 Ci = 37 GBq) intravenously and killed 1 hr later. Aliquots of plasma were taken for the determination of plasma water specific activity and aliquots of liver were taken for isolation of the digitonin-precipitable sterols. Rates of sterol synthesis (newly synthesized sterol content) were expressed as the nmoles of [^{3}H]water incorporated into digitonin-precipitable sterols per hour per gram of liver (nmol/hr per g).

Analytical Procedures. Plasma LDL–cholesterol concentrations were determined in the density range 1.020–1.055 g/ml. The cholesterol content of this fraction, as well as the total plasma cholesterol concentration, was measured as described (15). The hepatic content of free and esterified cholesterol was measured using silicic acid/Celite columns (18).

Calculations. Where appropriate, mean values ± 1 SEM are given and significance of differences between means was tested at the $P < 0.05$ level. Data points describing the rates of hepatic receptor-mediated LDL uptake at different concentrations of LDL–cholesterol in the plasma were fitted to curves having the general formula

$$J = 0.5\, D/R\{C_1 + K_m + RJ^m/D - [(C_1 + K_m + RJ^m/D)^2 - 4C_1(RJ^m/D)]^{1/2}\},$$

which describes the relationship between the rate of LDL uptake (J) and the concentration of LDL–cholesterol in the plasma (C_1) in terms of the resistance (R) encountered by the solute in moving from the plasma to the transport sites, the diffusion coefficient (D), and the Michaelis constant (K_m) and maximal transport velocity (J^m) of the receptor-mediated system (19, 20). In Fig. 3 these curves are shown as shaded areas representing ±2 SD from the mean curves.

RESULTS

To make any quantitative judgments as to the effect of a given dietary manipulation on the transport of LDL by the liver, it is necessary to have detailed information on the characteristics of both receptor-dependent and receptor-independent LDL transport at different circulating levels of LDL and at various concentrations of other lipoproteins in the plasma. Therefore, two groups of preliminary experiments were undertaken to define the kinetics of hepatic LDL transport in male hamsters fed only the low-cholesterol, low-triacylglycerol control diet. As illustrated in Fig. 1*A*, in such animals the plasma LDL level could be abruptly elevated and maintained at a new value for 4 hr by the primed-continuous infusion of homologous hamster LDL. Groups of such animals were then killed at hourly intervals and the accumulation of LDL in the liver was measured. At any steady-state concentration of LDL in the plasma, the transport of LDL into the liver was linear with respect to time (Fig. 1*B*). Two points warrant emphasis. First, the rates of hepatic LDL clearance (the slopes of the lines in Fig. 1*B*) decreased progressively from 120 μl/hr per g to 95 and 35 μl/hr per g as the concentration of LDL–cholesterol in the plasma was raised from the normal value of about 20 mg/dl to 59 and 240 mg/dl, respectively. Second, at any concentration of plasma LDL, the rate of accumulation of the lipoprotein in the liver was constant over the 4-hr interval (Fig. 1*B*), indicating that during the period that measurements were being made, elevation of the plasma LDL–cholesterol level did not alter the rate of hepatic LDL transport.

In similar experiments with a larger number of animals fed control diet, the rate of hepatic LDL uptake was measured as the plasma LDL–cholesterol concentration was varied over a very large range. Furthermore, these measurements were made in animals infused either with homologous hamster LDL, to measure both receptor-dependent and receptor-independent hepatic LDL uptake, or with methyl-hLDL, to

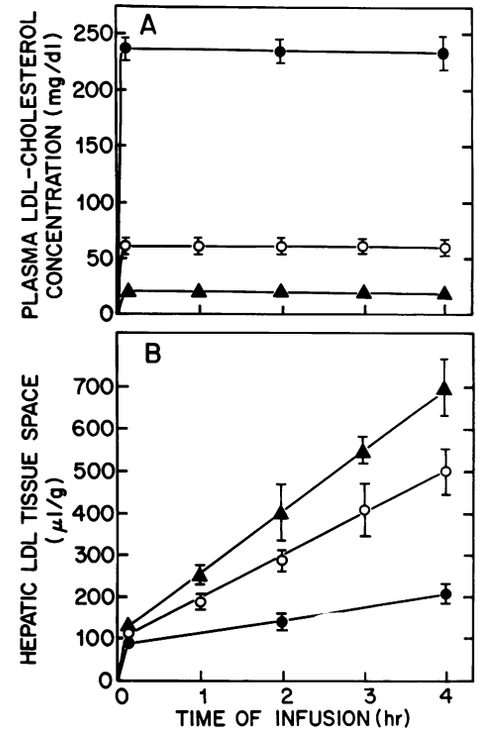

FIG. 1. Representative data showing the plasma LDL–cholesterol concentrations and rates of hepatic LDL uptake as a function of the time of infusion of LDL. Groups of animals were given various amounts of LDL, also containing [^{14}C]sucrose-LDL, as a bolus followed by a continuous infusion so as to either maintain the concentration of LDL–cholesterol at the normal level of about 20 mg/dl (▲) or abruptly increase it to 59 (○) or 240 (●) mg/dl over a 4-hr period (*A*). Groups of 6 animals were then killed at hourly intervals and the tissue space of LDL in the liver was determined (*B*). The clearance rate of LDL by the liver can be calculated from the slope of each of these lines and decreased markedly with the increase in plasma LDL–cholesterol concentration.

measure only receptor-independent uptake (2, 7, 12). As illustrated in Fig. 2, when the plasma LDL–cholesterol concentration was increased from 20 to nearly 500 mg/dl, hepatic clearance of homologous LDL decreased from approximately 120 to only 35 μl/hr per g. In contrast, the clearance of methyl-hLDL was constant at 9 ± 1 μl/hr per g. The absolute mass of LDL–cholesterol taken up by the liver at any plasma LDL–cholesterol concentration could be calculated by multiplying each of the clearance values shown in Fig. 2*A* by the plasma LDL–cholesterol level found in the same animal. These data, shown in Fig. 2*B*, illustrate that the amount of LDL–cholesterol taken up by the liver by receptor-independent transport mechanisms increased as a linear function of the plasma LDL–cholesterol concentration. When this component was subtracted from the kinetic curve for total LDL transport, the curve for saturable, receptor-mediated LDL uptake in the liver was obtained and manifested an apparent K_m value of about 85 ± 11 mg/dl and a maximal transport velocity of 131 ± 14 μg/hr per g. Thus, these curves define the kinetics of LDL transport in the liver of control hamsters when the concentration of LDL alone is selectively elevated.

However, in the animals fed the three experimental diets (see *Methods*) for 30 days, there were significant elevations of plasma cholesterol levels both in the LDL density range and in other lipoprotein classes (Table 1). In theory, these other lipoproteins, particularly those in the very low and intermediate density classes, might compete with LDL for receptor-dependent uptake into the liver. To test this possibility, plasma was harvested from animals fed the three experimental diets for 30 days and all lipoproteins with a density <1.21 g/ml were isolated. Trace quantities of [^{14}C]sucrose-LDL were added and various amounts of these three pools of lipoproteins were then infused into control hamsters and rates of LDL transport were measured at varying plasma concentrations of LDL–cholesterol. The data derived from these measurements were used to construct the kinetic curves shown as shaded areas in Fig. 3. Thus, these curves define the rates of LDL transport into the liver of control hamsters under circumstances where the animals also received the full complement of non-LDL lipoproteins found in the plasma of the groups of animals fed the three experimental diets. It is apparent that these three sets of kinetic curves are essentially identical to the transport curves generated with the infusion of LDL alone (Fig. 1), so the presence of these non-LDL lipoprotein fractions did not significantly alter the kinetics of LDL transport.

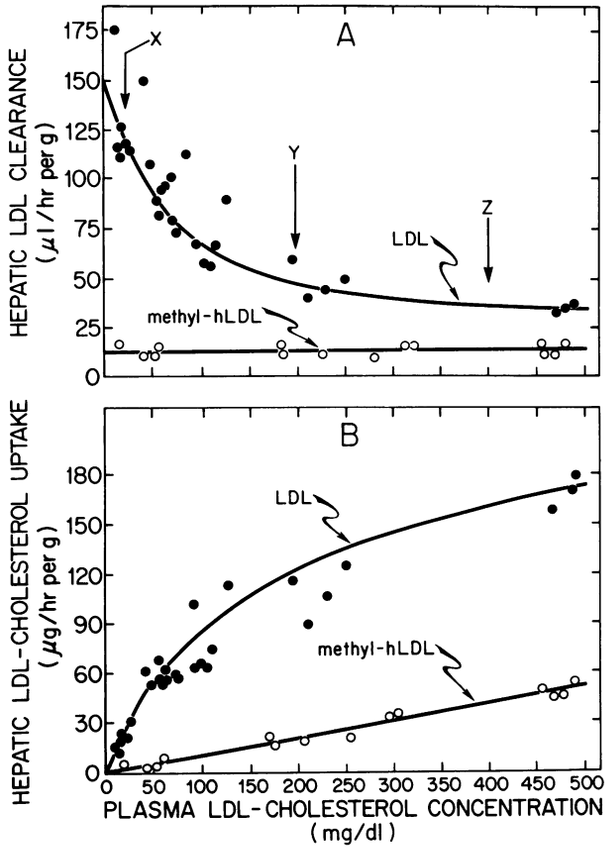

FIG. 2. Rates of hepatic LDL clearance and LDL–cholesterol uptake as a function of the concentration of LDL–cholesterol in the plasma. (*A*) The clearance rates for both homologous LDL (●) (receptor-dependent and receptor-independent clearance) and methyl-hLDL (○) (receptor-independent clearance) for individual animals as a function of the concentration of LDL-cholesterol found in the same animal. As shown by the arrows at X, Y, and Z, receptor-dependent transport accounted for 93% of the uptake at normal plasma LDL levels but only 78% and 60% when the plasma LDL–cholesterol concentration was raised to 200 and 400 mg/dl, respectively. (*B*) Each clearance value shown in *A* has been multiplied by the concentration of LDL–cholesterol present in the plasma of that animal to give the rate of hepatic LDL–cholesterol uptake for both total LDL transport and the receptor-independent component.

With these curves defined, it was now possible to determine the effects of triacylglycerol in the diet on hepatic cholesterol metabolism. As summarized in Table 1, the addition of only 0.12% cholesterol to the diet raised the plasma cholesterol concentration from 84 mg/dl to 126 and 234 mg/dl, respectively, at 3 and 30 days of feeding. The plasma LDL–cholesterol concentration also increased from 25 mg/dl to 48 and 82 mg/dl, respectively. At the same time there was marked suppression of hepatic cholesterol synthesis and an increase in the level of cholesteryl esters in the liver to 4.0 and 14.0 mg/g at 3 and 30 days, respectively. Coincident with these changes, receptor-dependent hepatic LDL clearance decreased from 112 μl/hr per g to 100 and 36 μl/hr per g, respectively, while receptor-independent LDL clearance remained constant at about 9 μl/hr per g. The addition of 20% polyunsaturated triacylglycerol to the cholesterol-containing diet had essentially no additional effect on any of these parameters, except that the rate of hepatic cholesterol synthesis was less suppressed.

In contrast, the addition of 20% saturated triacylglycerol to the diet resulted in striking alterations in cholesterol metabolism in these animals. After only three days of feeding, receptor-dependent LDL uptake by the liver declined from 112 to 25 μl/hr per g and the plasma LDL–cholesterol concentration increased 4-fold. After 30 days of feeding, the plasma LDL–cholesterol concentration reached 175 mg/dl and receptor-dependent LDL clearance declined to nearly undetectable levels, although receptor-independent clearance again remained constant at about 10 μl/hr per g. These changes occurred under circumstances where there was a significantly lower level of cholesteryl esters and a higher rate of cholesterol synthesis in the liver (compared to the animals receiving cholesterol alone).

The significance of these changes in LDL clearance can only be appreciated when these data are superimposed upon the standard kinetic curves for hepatic transport, as has been done in Fig. 3. After 3 days of feeding either cholesterol alone (Fig. 3 *A* and *B*) or cholesterol plus polyunsaturated triacylglycerol (*C* and *D*), the plasma LDL–cholesterol concentration doubled but the clearance rates fell within the kinetic curves for normal LDL transport. Only after 30 days of feeding did the clearance values fall slightly below the kinetic curves, indicating that there had been about a 30% reduction in LDL receptor activity. With saturated-triacylglycerol feeding, however, by 30 days almost no receptor-dependent LDL clearance was detectable (Fig. 3*E*).

Table 1. Low density lipoprotein metabolism in the liver of hamsters fed polyunsaturated or saturated triacylglycerol

Diet	Time on diet, days	Plasma cholesterol concentration, mg/dl	Plasma LDL-cholesterol concentration,* mg/dl	Receptor-dependent hepatic LDL clearance rate,† μl/hr per g	Hepatic cholesteryl ester concentration, mg/g	Hepatic cholesterol synthesis rates,‡ nmol/hr per g
Control	0	84 ± 4	25 ± 2	112 ± 9	0.7 ± 0.1	48 ± 12
Cholesterol	3	126 ± 6	48 ± 3	100 ± 8	4.0 ± 0.2	7 ± 1
	30	234 ± 14	82 ± 5	36 ± 5	14.0 ± 1.0	6 ± 1
Cholesterol plus PUT	3	114 ± 8	42 ± 4	101 ± 9	4.2 ± 0.3	18 ± 2§
	30	202 ± 17	69 ± 6	42 ± 6	13.1 ± 1.0	15 ± 1§
Cholesterol plus ST	3	204 ± 15§	104 ± 8§	25 ± 3§	2.4 ± 0.2§	22 ± 2§
	30	601 ± 35§	175 ± 10§	5 ± 2§	7.0 ± 1.0§	20 ± 1§

Groups of six animals were fed ground rodent diets containing 0.12% cholesterol, 0.12% cholesterol plus 20% polyunsaturated triacylglycerols (PUT), or 0.12% cholesterol plus 20% saturated triacylglycerols (ST) for 3 or 30 days. Control animals received only the ground rodent diet. All data represent mean values ± 1 SEM.

*LDL-cholesterol is defined as that which floats in the density range 1.020–1.055 g/ml.

†Calculated by subtracting the receptor-independent component from the rate of total hepatic LDL uptake.

‡Expressed as nmol of [^{3}H]water incorporated into digitonin-precipitable sterols *in vivo* per hr per g.

§Significantly different ($P < 0.05$) from the comparable values found in the animals fed cholesterol alone.

Thus, as shown in Fig. 3*F*, the uptake of LDL-cholesterol by the liver was essentially the same (about 30 μg/hr per g) in control and triacylglycerol-fed animals; however, in the control animals this process was 90% mediated by LDL receptors, whereas after saturated-triacylglycerol feeding it was 90% mediated by receptor-independent uptake. However, to achieve this parity of hepatic LDL uptake, it was necessary for the plasma LDL-cholesterol levels to increase 7-fold, from 25 to 175 mg/dl.

DISCUSSION

It has been appreciated for years that the relative content of saturated and polyunsaturated triacylglycerols in the diet significantly affects the circulating levels of LDL-cholesterol in man (21–23). In general, it has been shown that at least small amounts of cholesterol must be present in the diet in order to show a differential effect of polyunsaturated and saturated fat on serum lipids. Furthermore, the incremental rise in plasma cholesterol levels produced by feeding saturated lipid appears to be greater than the decrement produced by polyunsaturated-triacylglycerol feeding (23). Thus, the effects reported here in the hamster are qualitatively identical to those reported in man, although quantitatively the effects are much more pronounced. Presumably this results from the fact that the liver in the male hamster has such a limited capacity to respond to changes in cholesterol flux (7) and that the difference in the degree of saturation of the triacylglycerols employed in this study was much greater (iodine numbers of 4 and 130) than is possible in human experiments.

These studies also point up the complexity of interpreting the effects of dietary additions on plasma LDL levels, even when LDL transport rates are measured directly. For example, since receptor-dependent uptake plays a major role in the liver in LDL degradation, the absolute hepatic clearance rate decreases markedly when the plasma LDL-cholesterol concentration is raised and the transport sites become saturated (Fig. 2). Hence, in any situation in which the plasma

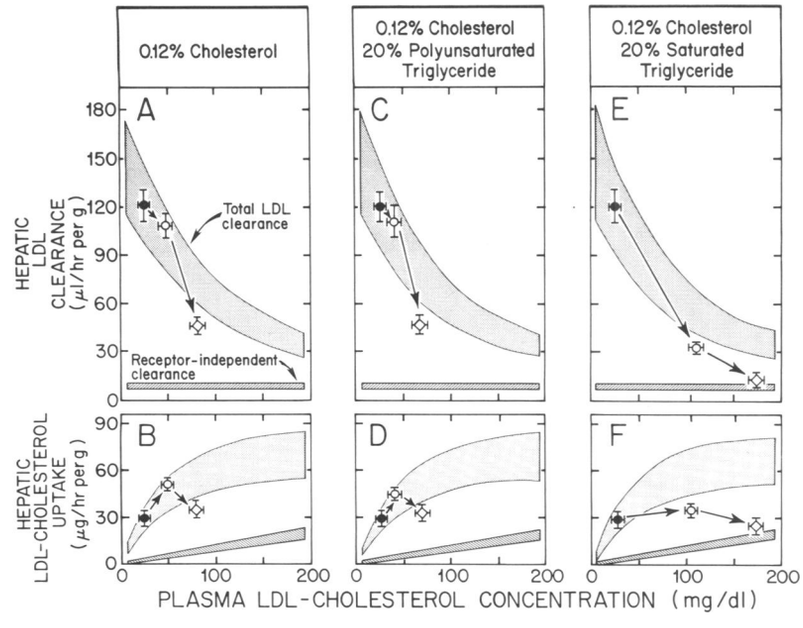

FIG. 3. Hepatic clearance and LDL-cholesterol uptake in animals fed a cholesterol-containing diet without (*A* and *B*) or with added polyunsaturated (*C* and *D*) or saturated (*E* and *F*) triacylglycerol. The shaded areas represent the kinetic curves for total (stippled) and receptor-independent (hatched) LDL clearance and uptake determined in the presence of the elevated concentrations of non-LDL lipoproteins found in the plasma of the three respective groups of experimental animals. The individual points superimposed on these standard curves show the mean values ± 1 SEM for these two parameters in six animals maintained on each of the diets for 0 days (●), 3 days (○), and 30 days (◇).

LDL–cholesterol level is elevated, reduction in the hepatic clearance rate (or fractional catabolic rate in the whole animal) cannot be taken as evidence that there has been suppression of LDL-receptor activity. Such data are interpretable only when referred to the appropriate kinetic curves describing LDL-transport in that experimental model (Fig. 3).

In this study, feeding saturated triacylglycerol in the presence of small quantities of cholesterol markedly elevated the plasma LDL–cholesterol levels. Had this effect been due solely to overproduction of LDL, the hepatic clearance of LDL would have been reduced to only 40–45 μl/hr per g. In fact, it was reduced to much lower levels and, furthermore, the receptor-dependent fraction was reduced nearly to zero. Hence, as has been described with cholestyramine and cholesterol feeding (7, 24), these various dietary manipulations affect the level of LDL-receptor activity but have no effect on the uptake of LDL–cholesterol by receptor-independent mechanisms. Finally, several lines of evidence suggest that this effect of saturated triacylglycerol is not merely a manifestation of increased dietary cholesterol absorption. Saturated lipids actually have been reported to reduce cholesterol absorption (relative to polyunsaturated triacylglycerol feeding), a finding that is consistent with the observations in this study that the level of cholesterol esters in the liver was significantly lower and the rate of cholesterol synthesis was higher in the animals fed the saturated lipids than in those fed cholesterol alone. The possibility exists, therefore, that saturated triacylglycerol may exert its marked effect on LDL-receptor activity through an effect on the subcellular distribution of cholesterol within the hepatocyte, rather than by a gross change in cholesterol balance throughout the cell.

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