

Mechanisms of triglyceride-lowering effect of an HMG-CoA reductase inhibitor in a hypertriglyceridemic animal model, the Zucker obese rat

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Abstract Inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase have been approved for treatment of hypercholesterolemia in humans. This class of therapeutic agents, in addition to lowering plasma cholesterol, reduces plasma triglyceride levels. We have investigated the mechanism of triglyceride-lowering effect of lovastatin in the hypertriglyceridemic state by using a rodent model of hypertriglyceridemia and obesity, the Zucker obese (fa/fa) rat. Lovastatin treatment (4 mg/kg), as compared to placebo, caused a 338% reduction in plasma triglyceride (146 ± 5 vs. 494 ± 76 mg/dl), a 58% decrease in total cholesterol (99 ± 13 vs. 156 ± 18 mg/dl), and a 67% reduction in high density lipoprotein (HDL)-cholesterol (69 ± 8 vs. 115 ± 15 mg/dl). The fall seen in plasma triglyceride was due to a decrease in hepatic secretion of very low density lipoproteins (VLDL), determined after blocking the clearance of triglyceride-rich lipoproteins with Triton WR-1339. Lovastatin treatment did not affect either the activities of hepatic lipogenic enzymes, glucose-6-phosphate dehydrogenase, or malic enzyme, or the activities of the lipolytic enzymes of adipose tissue, lipoprotein lipase, or liver, hepatic triglyceride lipase. Supplementation of mevalonolactone in the diet partially reversed the changes in plasma triglyceride (265 ± 37 vs. 146 ± 5 mg/dl), but not in total or HDL-cholesterol. ■ These data demonstrate that, in the hypertriglyceridemic Zucker rat model, HMG-CoA reductase inhibitors reduce the rate of secretion of VLDL and this effect can be partially reversed by administration of mevalonolactone.—**Kasim, S. E., R. C. LeBoeuf, S. Khilnani, L. Tallapaka, D. Dayananda, and K-L.C. Jen.** Mechanisms of triglyceride-lowering effect of an HMG-CoA reductase inhibitor in a hypertriglyceridemic animal model, the Zucker obese rat. *J. Lipid Res.* 1992. **33**: 1–7.

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Inhibitors of the rate limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in addition to lowering plasma total and low density lipoprotein (LDL) cholesterol, reduce plasma triglyceride and very low density lipo-

protein (VLDL) concentrations (1–3). Since HMG-CoA reductase does not play a direct role either in synthesis or in hydrolysis of triglycerides, the mechanism of this latter finding is not clear. It has been proposed that inhibition of HMG-CoA reductase leads to a reduction in the concentration of cholesterol in the hepatocytes, and therefore, up-regulation of LDL-receptors (4). Since these receptors bind and internalize not only LDL but also VLDL remnants, plasma triglyceride is reduced (1). Another putative mechanism is based on the concept that cholesterol is an obligatory component for normal assembly of VLDL (5, 6). Inhibition of cholesterol biosynthesis limits the availability of cholesterol for production and secretion of VLDL.

We thought that use of a hypertriglyceridemic model could facilitate the understanding of the alterations in triglyceride metabolism, and therefore, used the Zucker obese (fa/fa) rat. This animal model is characterized by primary hypertriglyceridemia, which is due to overproduction of VLDL without any defect in its clearance (7). The following questions were addressed: 1) Does lovastatin reduce plasma triglyceride levels in the hypertriglyceridemic state? 2) Is the hepatic secretion rate of VLDL altered? 3) Is there a change in the lipid composition of newly secreted VLDL? 4) Does lovastatin alter the lipid content of the liver? 5) Does

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; LpL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; LOV, lovastatin; PL, placebo; MVA, mevalonolactone; FFA, free fatty acids; ME, malic enzyme; G-6-PDH, glucose-6-phosphate dehydrogenase.

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lovastatin suppress the activities of hepatic lipogenic enzymes? 6) Are the activities of lipolytic enzymes of adipose tissue or the liver stimulated? 7) Can restoration of cholesterol synthesis reverse the changes in plasma and/or liver lipids induced by lovastatin?

EXPERIMENTAL PROCEDURES

Animals

Eight- to thirteen-week-old male Zucker fa/fa rats were purchased from Charles River Laboratories (Boston, MA). Each rat was housed in a stainless steel hanging cage in a temperature- and light cycle-controlled colony room (lights on 0700–1900 h) and had free access to water and Purina Rodent Chow (Ralston Purina Co., St. Louis, MO). After matching for age and baseline plasma lipid levels, rats were assigned to either lovastatin (LOV) or placebo (PL) treatment groups. The former group received daily subcutaneous injections of lovastatin (4 mg/kg) and the latter received ethanol-propylene glycol 1:1 (v/v). This dose, which is fourfold higher than the maximal therapeutic dose used in humans, was selected because of the observations of Kasiske et al. (8) who noticed the triglyceride-lowering effect of lovastatin in the Zucker rats while studying its effect on the renal failure. On the ninth day of lovastatin or placebo treatment, MVA (1%, w/w) was added to the diets of a subgroup of animals in each treatment arm. Four days later all the animals were killed. Total duration of the study was 13 days.

Determination of various lipids and enzymes in plasma and in tissues

On the morning of the experiment, food was removed. Four hours later the animals were killed with sodium pentobarbital (120 mg/kg, intraperitoneally). Blood was collected by cardiac puncture in EDTA-containing tubes kept on ice. Plasma was separated immediately and used for the measurements of triglyceride, total and high density lipoprotein (HDL)-cholesterol. The liver was removed and frozen immediately at -70°C for determination of triglyceride, total and free cholesterol, cholesteryl ester, phospholipids, glucose-6-phosphate dehydrogenase (G-6-PDH), malic enzyme (ME), and hepatic triglyceride lipase (HTGL). Parametrial adipose tissue was removed, acetone-ether powders were prepared and stored at -70°C for determination of the lipoprotein lipase (LPL) activity.

Triton WR-1339 experiments

For these experiments, rats were fasted overnight to eliminate chylomicrons from the plasma. On the next morning, the rats were anesthetized with pentobarbital

and an intravenous catheter was inserted into the jugular vein. Rats were kept warm on heating pads and remained anesthetized throughout the study. After obtaining baseline samples, Triton WR-1339 (Tyloxapol, Sigma Chemical Co., St. Louis, MO), a detergent that blocks the hepatic and peripheral clearances of triglyceride-rich lipoproteins, was dissolved in normal saline (300 mg/ml) and injected through the same catheter at a dose of 400 mg/kg. Blood samples for measurement of triglyceride and cholesterol were obtained before and 60 and 120 min after the injection of Triton WR-1339. An aliquot of the plasma was used for the separation of VLDL ($d < 1.006$ g/ml) by ultracentrifugation. The lipid content of VLDL was also analyzed. The rate of accumulation of triglyceride was calculated using the following formula (9):

$$\text{Triglyceride entry rate (mg/min)} = \frac{\text{triglyceride increment (mg/ml)} \times \text{plasma volume (ml)}}{\text{time (min)}}$$

Lipid determinations

Triglyceride was determined enzymatically by a kit method (Sigma). Current interassay coefficient of variation was 3.6% for triglyceride. Cholesterol was also measured enzymatically (Boehringer Mannheim). Free and esterified fractions were differentiated by serial incubation of plasma first with cholesterol oxidase then cholesterol esterase. Our coefficient of variation for the total cholesterol assay was 1.9%. HDL-cholesterol was determined by method of Warnick, Benderson, and Albers (10) using dextran sulfate-magnesium chloride. Phospholipids were measured using the method of Dittmer and Wells (11). In the liver extracts cholesteryl ester and free cholesterol fractions were separated by thin-layer chromatography (TLC) and quantified by scanning (Dual Wavelength TLC Scanner CS-930, Shimadzu, Japan) (12).

Determination of LPL and HTGL activities

Acetone-ether powders of the adipose tissue and homogenates of the liver were prepared. An aliquot (0.1 ml) of the enzyme source was incubated with the substrate (13) in a total volume of 0.2 ml at 37°C for 30 min. At the end of incubation, the FFA released were extracted with a mixture of chloroform-methanol-heptane 1:3:4 followed by potassium carbonate buffer, pH 10.5. One mU activity is defined as the release of 1 nmol FFA per min. Each assay included a high and a low enzyme activity reference standard. The coefficient of variation for both assays was less than 2%.

Determination of G-6-PDH and ME activities

Two grams of liver from each rat was homogenized and supernatant was prepared according to the proce-

dures described by Cleary (14). Supernatants were assayed for G-6-PDH activity by the method of Glock and McLean (15) and ME activity as described by Ochoa (16). Both of these assays are based upon the spectrophotometric measurement of NADPH generated from NADP.

Statistical analysis

Mean and standard error of means were reported. Analysis of variance (ANOVA) with repeated measures was used to analyze body weight and food. ANOVA was also performed to compare all other parameters between the four treatment groups. Significance level was set at $P < 0.05$. When an overall significance level was observed, the least significant difference *t*-tests were carried out to identify the groups that contributed the difference. Due to the large variation in plasma triglyceride levels a nonparametric comparison (Kruskal-Wallis rank test) was performed on this parameter.

RESULTS

Effect of lovastatin on plasma lipid levels

Lovastatin treatment or dietary supplementation of MVA did not affect the amount of daily food intake. Rats that received lovastatin had the following reductions in plasma lipids as compared to placebo-treated rats: 338% in triglyceride, 58% in total cholesterol, and 67% in HDL-cholesterol. HDL-triglyceride did not change significantly (Table 1).

Changes in hepatic lipid concentrations

To determine whether the decrease in plasma triglyceride was accompanied by either a depletion or a retention of triglyceride in the liver, hepatic triglyceride concentration was measured after extracting the nonpolar lipids with chloroform-methanol. After treatment with lovastatin, triglyceride content of the liver was increased by 64% (Table 2). Free cholesterol, cholesteryl ester, and phospholipid concentrations did not change significantly.

Triton WR-1339 experiments

To directly test the possibility that the fall in plasma triglyceride and the increase in liver triglyceride seen after lovastatin treatment may be due to a decrease in the hepatic secretion of VLDL, clearance of triglyceride-rich lipoproteins was blocked by intravenous injection of Triton WR-1339. During the next 2 h, rates of plasma TG entry were 0.53 mg/min in lovastatin-treated rats and 1.35 mg/min in placebo-treated rats ($P < 0.05$) (Fig. 1). At 0 min and 120 min VLDL was isolated by ultracentrifugation. Lovastatin treatment decreased the triglyceride, free cholesterol, and phospholipid content of newly secreted VLDL (Table 3). In newly secreted VLDL, molar ratio of triglyceride either to total or to free cholesterol was slightly lower in lovastatin-treated rats (6.4 and 8.6, respectively, for placebo and 5.1 and 6.2 for lovastatin treatment group). The opposite was true for the ratio of triglyceride to cholesteryl ester (25.7 in placebo and 32.2 in lovastatin treatment group).

Effect of MVA supplementation on plasma and liver lipids

To determine whether the changes in plasma and liver lipids were related to the block in cholesterol biosynthesis or to an independent effect of lovastatin, a group of rats were fed MVA (1%, w/w) in the diet during the last 4 days of the study. Prior to the initiation of MVA supplementation, blood samples were obtained by retroorbital sinus puncture and triglyceride levels were measured. The mean plasma triglyceride level was 134 ± 5 mg/dl in LOV group and increased to 265 ± 37 mg/dl after MVA ($P < 0.005$). Concentrations of hepatic lipids did not change. These data suggested that the lovastatin-induced decrease in VLDL secretion is related to the changes in cholesterol metabolism.

Changes in the activities of lipogenic and lipolytic enzymes

Lovastatin treatment did not alter the activities of either lipogenic enzymes (ME, G-6-PDH) or lipolytic enzyme (HTGL) of the liver. Activities of these en-

TABLE 1. Effects of lovastatin treatment and dietary mevalonolactone supplementation on body weight and plasma lipids

	PL	LOV	LOV + MVA	PL + MVA	P_1	P_2	P_3	P_4
Body weight (g)	611 ± 27	565 ± 25	527 ± 14	596 ± 32	N.S.	N.S.	N.S.	N.S.
Plasma								
TG(mg/dl)	494 ± 76	146 ± 5	265 ± 37	431 ± 55	0.005	0.05	N.S.	0.01
TC(mg/dl)	156 ± 18	99 ± 13	88 ± 4	116 ± 11	0.05	N.S.	N.S.	0.001
HDL-C(mg/dl)	115 ± 15	69 ± 8	57 ± 4	81 ± 8	0.05	N.S.	0.06	0.001
HDL-TG(mg/dl)	60 ± 3	43 ± 4	41 ± 2	57 ± 3	0.005	N.S.	N.S.	0.001

Values are given as mean ± SEM (n = 5). Abbreviations: PL, placebo; LOV, lovastatin; MVA, mevalonolactone; TG, triglyceride; C, cholesterol; TC, total cholesterol. P_1 = PL vs. LOV; P_2 = LOV vs. LOV + MVA; P_3 = PL vs. PL + MVA; P_4 = PL vs. LOV + MVA.

TABLE 2. Effects of lovastatin treatment and dietary mevalonolactone supplementation on liver weight and lipids

	PL	LOV	LOV + MVA	PL + MVA	P ₁	P ₂	P ₃	P ₄
Weight (g)	21.8 ± 1.6	22.5 ± 1.2	21.6 ± 1.7	21.2 ± 1.4	N.S.	N.S.	N.S.	N.S.
TG(mg/g)	13.9 ± 0.8	22.8 ± 0.8	20.4 ± 1.7	14.2 ± 2.5	0.0001	N.S.	N.S.	0.01
TC(mg/g)	3.03 ± 0.79	2.47 ± 0.30	3.47 ± 1.20	3.38 ± 1.08	N.S.	N.S.	N.S.	N.S.
FC(mg/g)	1.61 ± 0.38	1.71 ± 0.39	1.43 ± 0.38	1.20 ± 0.54	N.S.	N.S.	N.S.	N.S.
CE(mg/g)	1.42 ± 0.42	0.77 ± 0.29	2.04 ± 0.84	2.15 ± 0.56	N.S.	N.S.	N.S.	N.S.

Values are given as mean ± SEM (n = 5). Abbreviations: PL, placebo; LOV, lovastatin; MVA, mevalonolactone; TG, triglyceride; TC, total cholesterol; FC, free cholesterol; CE, cholesteryl ester. P₁ = PL vs. LOV; P₂ = LOV vs. LOV + MVA; P₃ = PL vs. PL + MVA; P₄ = PL vs. LOV + MVA.

zymes in lovastatin- versus placebo-treated rats were as follows (mU/g wet weight): ME, 1.3 ± 0.1 vs. 1.1 ± 0.1; G-6-PDH, 2.9 ± 0.2 vs. 3.2 ± 0.3; HTGL, 2540 ± 160 vs. 2970 ± 180. Activity of the adipose tissue LPL was not affected (97 ± 8 mU/g wet weight in lovastatin- vs. 79 ± 23 in placebo-treated rats). These findings suggested that lovastatin probably does not significantly alter either the synthesis or hydrolysis of triglycerides.

DISCUSSION

Inhibitors of HMG-CoA reductase block the rate-limiting step in cholesterol synthesis and are used primarily to reduce plasma LDL-cholesterol levels. Studies in humans and animals demonstrated that these agents also lower plasma triglyceride (1–3, 6, 17–20). The reports that investigated the mechanisms of triglyceride-reducing effect of HMG-CoA reductase inhibitors in animal models are summarized in Table 4. Earlier studies of Endo et al. (17), which investigated the effect of compactin in mice and rats, did not show any change in plasma lipids in normolipidemic animals. In rats with primary or fructose-induced hypertriglyceridemia, a small decrease (25%) was seen in triglyceride levels without any change in hepatic secretion of VLDL-triglyceride. The report of Yoshino et al. (18) confirmed the triglyceride-lowering effect of pravastatin in the Wistar rats, even in the absence of any cholesterol-lowering action. In these experiments pravastatin decreased hepatic secretion rate of VLDL in the fed state, but not during fasting. Studies of Khan et al. provided in vivo (19) and in vitro (6) evidence to support that HMG-CoA reductase inhibitors interfere with the secretion of VLDL from the liver in the normal rat, without altering its clearance. Furthermore, supplementation of cholesterol partially reverses this defect. Finally, Hirano et al. (20) investigated the effect of pravastatin in rats with hyperlipidemia due to nephrosis and showed a significant decrease in triglyceride secretion rate without any change in the removal. Since the results of these studies seem to provide variable results depending on the baseline trigly-

ceride levels and the feeding state of the animals, we decided to investigate the effects of HMG-CoA reductase inhibitors on metabolism of VLDL in a model of primary hypertriglyceridemia, the Zucker fa/fa rat. Furthermore, the previous studies had used high doses of these agents, 40 to 500 mg/kg per day, raising the possibility that the triglyceride-lowering effect of HMG-CoA reductase inhibitors was limited to this dose range. Therefore, we used a much lower dose of lovastatin (4 mg/kg) which is still fourfold higher than the maximal therapeutic dose in humans. This dose was selected based upon the report of Kasiske et al. (8), who noted the triglyceride-lowering effect of lovastatin while studying its effects on renal failure.

In addition to the concentration of plasma and liver lipids and changes in hepatic secretion rate of VLDL, we determined the changes in major lipogenic and

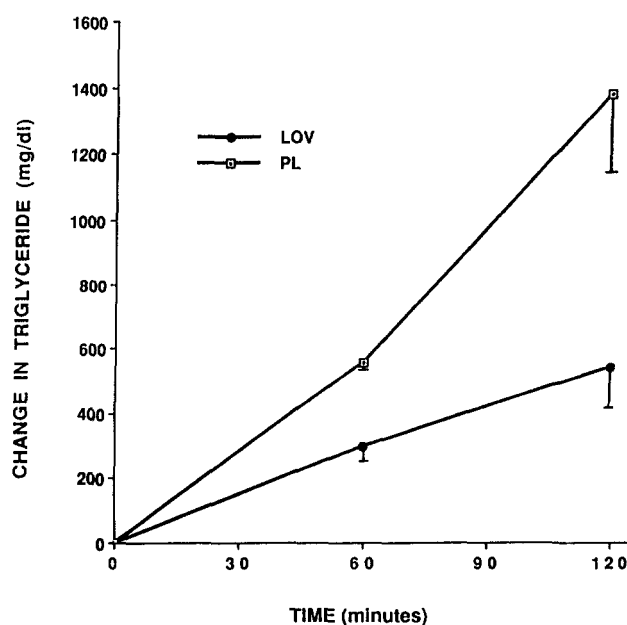


Fig. 1. Changes in plasma triglyceride after injection of Triton WR-1339, in placebo (PL) and lovastatin (LOV) treated animals (n = 4). Baseline triglyceride values were 187 ± 52 mg/dl in LOV- and 316 ± 22 mg/dl in PL-treated groups.

TABLE 3. Effect of lovastatin treatment on the lipid composition of VLDL before and after injection of Triton WR-1339

	0 Min				120 Min			
	TG	FC	CE	Phospholipid	TG	FC	CE	Phospholipid
PL(mg/dl)	139 ± 34	7.8 ± 2.0	2.8 ± 2.3	48.6 ± 14.5	936 ± 95	47.6 ± 3.7	16.0 ± 6.7	294 ± 30
(%)	70.1	3.9	1.4	24.5	72.4	3.7	1.2	22.7
LOV(mg/dl)	42 ± 7*	2.4 ± 0.5	0.27 ± 0.3	5.0 ± 3.0	285 ± 105*	20.3 ± 5.1**	4.0 ± 1.7	109 ± 22*
(%)	84.5	4.8	0.5	10.1	68	4.9	1.0	26.1

Values are given as mean ± SEM (n = 4). Abbreviations: TG, triglyceride; FC, free cholesterol; CE, cholesteryl ester; PL, placebo; LOV, lovastatin. *, $P < 0.05$; **, $P < 0.01$ when compared to placebo.

lipolytic enzyme activities. Our study confirmed the triglyceride-lowering action of lovastatin. An unexpected finding was that the decrease in plasma cholesterol (58%) was markedly less than the decrease in plasma triglyceride (338%). Furthermore, decreases seen in the triglyceride and cholesterol content of VLDL were much greater than those seen in HDL. These results suggest that the net effect of HMG-CoA reductase inhibitors on the plasma lipoproteins may differ depending on the characteristics of the lipoprotein metabolism of the species. In humans, where the major carrier of cholesterol is LDL, lovastatin lowers LDL-cholesterol and does not change or may even increase HDL. Whereas, in the Zucker rat, the major plasma cholesterol carriers are HDL and VLDL and lovastatin lowers both of these lipoproteins.

The decrease in plasma triglyceride was associated with an increase in hepatic triglyceride, suggesting that there may have been retention of triglycerides in the liver without any compensatory decrease in their production. Accordingly, activities of the hepatic lipogenic enzymes, ME and G-6-PDH, were not suppressed. The rate of hepatic VLDL secretion was measured directly by using Triton WR-1339, which blocks both hepatic and peripheral clearance of VLDL. The value of this test in the assessment of hepatic secretion rate of VLDL has been previously discussed (21). The finding of a slower accumulation of triglyceride in lovastatin-treated animals confirmed that the fall in plasma triglyceride was due to a decrease in the secretion of VLDL instead of an increase in the clearance of VLDL. In support of this, activities of HTGL and adipose tissue-LPL were not stimulated. The results of our study indicated that, in the state of primary hypertriglyceridemia, inhibitors of HMG-CoA reductase interfere with the hepatic secretion of VLDL without increasing the clearance rate, similar to that seen in the normal rats or in secondary hypertriglyceridemia.

Despite the marked increase in hepatic triglyceride concentration, there was no change in the hepatic total or free cholesterol levels. The decrease seen in cholesteryl ester was not statistically significant. Khan, Wilcox, and Heimberg (6) also reported no change in hepatic free cholesterol during lovastatin treatment in

normal Sprague Dawley rats, however, the fall in hepatic cholesteryl ester concentration was statistically significant in their study. The selective decrease seen in esterified cholesterol, despite the availability of substrate, free cholesterol, raises the possibility that lovastatin may suppress the activity of acyl-coenzyme A:cholesterol O-acyltransferase (ACAT). Ishida et al. (22) have demonstrated an inhibitory action of an HMG-CoA reductase blocker on intestinal ACAT. This apparent inhibition may have been secondary to the relative unavailability of the substrate. A recent report that investigated the effect of pravastatin on activity of ACAT in human liver did not find any inhibition (23).

The block of VLDL secretion despite the availability of hepatic free cholesterol suggests various possibilities. As suggested by Khan et al. (6), free cholesterol measured in the liver extracts may represent the cholesterol in the cell membrane, which is metabolically inactive. Whereas the cholesteryl ester pool may be in equilibrium with a metabolically active free cholesterol pool that is available for the assembly of VLDL. Alternatively, the triglyceride-lowering action of lovastatin may be independent of cholesterol biosynthesis. However, results of our MVA-feeding studies make the latter possibility unlikely. We have observed that supplementation of the diet with MVA for 4 days significantly raised the plasma triglyceride, but did not restore it to the level seen in placebo-treated controls. The failure of complete recovery of plasma triglyceride may be due to relatively short duration of MVA supplementation or may suggest the presence of additional regulatory factors. Studies of Khan et al. (19) also demonstrated that in lovastatin-treated rats, addition of cholesterol to the diet increased the plasma triglyceride level, further supporting the significant role of cholesterol in the assembly and secretion of VLDL. An interesting finding of our study was that MVA supplementation for 4 days did not alter cholesterol or triglyceride content of HDL. This may be due to the longer half life of HDL as compared to VLDL.

Finally, the effect of inhibition of HMG-CoA reductase on the lipid composition of VLDL was investigated. Lovastatin treatment decreased the secretion

TABLE 4. Summary of findings on the effects of HMG-CoA reductase inhibitors on metabolism of VLDL

Ref #	Animal Model	Agent	Dose mg/kg/day	Duration days	Results
6	Rat: Sprague-Dawley	Lov	80	7	Liver perfusion studies; Decreases in VLDL-TG, VLDL-C, and phospholipid; Decreases in hepatic TG and CE without any change in FC.
17	Rat: Fischer Donryu Wistar-Imamichi Mice: RFVL DDY	Comp	200-500	4-11	No overall hypocholesterolemic effect; No inhibition of C synthesis; Decrease in serum TG in some species.
18	Rat: Wistar	Prav	40	14	Decrease in plasma-TG without change in cholesterol; Decreases in VLDL-TG and VLDL-C; Decrease in VLDL secretion in the fed but not in fasted state.
19	Rat: Sprague-Dawley	Lov	80	7	Decreases in secretion of all VLDL lipids and TG synthesis; No change in VLDL clearance; Decrease in hepatic CE without any change in FC.
20	Rat: Wistar	Prav	80	7	Decrease in VLDL-TG, VLDL-C, and VLDL-apoB in nephrotic animals.

Abbreviations: Lov, lovastatin; Comp, compactin; Prav, pravastatin; VLDL, very low density lipoprotein; TG, triglyceride; C, cholesterol.

rates of all the lipid classes and slightly lowered the ratio of triglyceride to total and free cholesterol in the newly secreted particle.

In summary, findings of the present study 1) confirmed the triglyceride-reducing action of a HMG-CoA reductase inhibitor in a model of primary hypertriglyceridemia at a markedly lower dose than previously studied; 2) demonstrated that the decrease in hepatic secretion of VLDL occurs without any change in the activities of hepatic lipogenic enzymes; 3) showed that HMG-CoA reductase inhibitors do not stimulate the activity of HTGL or adipose tissue-LPL; and 4) suggested that restoration of cholesterol biosynthesis at least partially reverses the decrease in plasma triglyceride. It is not known, however, whether the triglyceride-lowering effect of lovastatin occurs through similar mechanisms in humans. ■■

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