VLDL Triglyceride Kinetics in Wistar Fatty Rats, An Animal Model of NIDDM

Effects of Dietary Fructose Alone or in Combination With Pioglitazone

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The effects of dietary fructose alone or in combination with a new oral agent, pioglitazone, on VLDL-triglyceride (TG) turnover were studied in genetically obese Wistar fatty rats characterized by hyperinsulinemia (7,488 ± 954 pmol/l), hyperglycemia (22.5 ± 1.4 mmol/l), and hypertriglyceridemia (4.39 ± 0.54 mmol/l). They had an increased hepatic TG production (16.2 ± 0.1 μmol/min; lean rats, 5.4 ± 0.3 μmol/min) as well as a longer half-life of VLDL-TG from lean donors (8.8 ± 1.4 min, lean recipients; 2.3 ± 0.9 min). In addition, in lean recipients, the half-life of VLDL-TG from fatty donors was longer than that from lean donors (4.80 ± 0.56 vs. 3.14 ± 0.23 min). Although feeding fructose into fatty rats did not change plasma glucose and insulin levels, it produced a twofold increase in TG levels (8.74 ± 1.15 mmol/l). This was associated with a 1.7-fold increase in TG production to 27.5 ± 1.2 μmol/min, while no significant change was found in the half-life of lean VLDL-TG in fructose-fed fatty recipients (10.9 ± 2.4 min) or in that of VLDL-TG from fructose-fed fatty donors in lean recipients (4.46 ± 0.76 min). Daily administration of pioglitazone (3 mg/kg body weight) in fructose-fed fatty rats ameliorated glycemia and triglyceridemia to the level of lean rats (8.1 ± 0.7 and 1.18 ± 0.05 mmol/l, respectively) and insulinemia to a lesser extent (2,712 ± 78 pmol/l). A fall in TG levels was associated with improvement of an impairment in the ability of fructose-fed fatty rats to remove lean VLDL-TG (half-life: 2.6 ± 0.6 min). Pioglitazone, however, produced no change in TG production (25.9 ± 2.7 μmol/min), the half-life of VLDL-TG from fructose-fed fatty donors in lean recipients (4.17 ± 0.38 min), or the activity of lipoprotein lipase and hepatic lipase in postheparin plasma. We conclude that in Wistar fatty rats *1*) hypertriglyceridemia is attributed to TG overproduction and impaired TG catabolism, and the latter is due to changes in both VLDL, such that they are less able to be removed, and changes in the nature of Wistar fatty rats, such that they are less able to remove VLDL-TG; *2*) fructose further increases hepatic TG production with a resultant deterioration in hypertriglyceridemia; *3*) pioglitazone normalizes TG levels by altering the physiology of the Wistar fatty rats in a manner that increases their ability to remove VLDL-TG from the circulation. *Diabetes* 45:806–811, 1996

Insulin resistance is a central pathophysiological feature of NIDDM. In addition, insulin resistance is a common metabolic abnormality in obesity, hypertension, dyslipidemia, and atherosclerosis (1). Nongenetic environmental factors, such as diet, produce a state of insulin resistance. Studies in rodents have shown that feeding fructose resulted in an impairment of insulin action in both the skeletal muscle and liver (2,3).

We have previously shown that feeding fructose to rodents produced an elevation of plasma triglyceride (TG) in diabetic (4,5) and nondiabetic rats (6,7) and that this was associated not only with an increase in the secretion of VLDL-TG from the liver (6,7) but also with defects in VLDL-TG catabolism from the circulation (4,5,8,9).

Thiazolidinediones are a new class of antidiabetic agents that appear to work by either mimicking or enhancing insulin action without stimulation of insulin secretion (10–12). They also have hypolipidemic effects (13–15). Therefore, this study was undertaken to characterize VLDL-TG kinetics in hypertriglyceridemia of Wistar fatty rats, an animal model of NIDDM (16), and to determine the effects of dietary fructose when used alone or in combination with pioglitazone.

RESEARCH DESIGN AND METHODS

Rat groups. Three groups of Wistar fatty rats and one group of Wistar lean rats aged 18 weeks at the beginning of the study, bred in the laboratory of Pharmaceutical Research Division, Takeda Chemical Industries, Osaka, Japan, were used throughout the study. The rats were maintained in individual cages on a 12:12-h light/dark cycle. Two groups of fatty rats had free access to rat food (CE-2, Oriental Yeast, Tokyo, Japan) and drinking water that contained 10% (wt/vol) fructose. The third group of fatty rats and group of lean rats were given ad libitum access to rat food and drinking water that contained no fructose (controls who were fed food). One group of fructose-fed fatty rats received daily administration of pioglitazone (3 mg/kg body weight, suspended in 0.5% methyl cellulose), started the same day as fructose feeding, for 21–23 days through a gastric tube into their stomach,

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HL, hepatic lipase; LPL, lipoprotein lipase; NEFA, nonesterified fatty acids; TG, triglyceride.

TABLE 1
Body weight and daily caloric intake

Groups	Lean controls	Fatty controls	Fructose-fed fatty rats	Fructose- and pioglitazone-fed fatty rats
Body weight (g)				
Starting	433 ± 4*	608 ± 8†	610 ± 11†	610 ± 7†
Final	427 ± 7*	621 ± 11†	655 ± 13§	706 ± 10‡
Weight gain (g/3 week)	−6 ± 5*	12 ± 6†	45 ± 3§	96 ± 9‡
Daily caloric intake (cal)				
Total	75 ± 2*	117 ± 4†	136 ± 3§	154 ± 6‡
From food	75 ± 2*	117 ± 4†	100 ± 2§	126 ± 5†
From fructose	none	none	37 ± 2*	28 ± 2†

Data are means ± SE of 11 rats in each group. Fructose was supplied in 10% drinking solution for 3 weeks. Pioglitazone (3 mg/kg body weight) was given intragastrically daily for 3 weeks. Caloric intake was calculated by the amount of food (3.45 cal/g) and fructose (4.0 cal/g) consumed. Means in the same row not sharing a common symbol are significantly different from each other at $P < 0.05$ or less.

whereas another group received vehicle alone. The amount of rat food and fructose consumed by each rat was measured for eight consecutive days. Plasma concentrations of glucose, insulin, TG, cholesterol, and nonesterified fatty acids (NEFA) were measured in the fed state at time intervals indicated in Table 2.

TG secretion rates. On the night of day 20, food was withdrawn. However, all rats were allowed access to drinking water until the end of the experiment. On day 21, between 9:00 A.M. and noon, the rate of TG secretion was measured by the Triton method as previously described by us (6,17). Rates of TG production determined by the Triton and tracer methods using [^{3}H]glycerol or [^{14}C]glycerol were the same (18).

The batch of Triton WR1339 (Nakarai Chemicals, Kyoto, Japan) used in this study has demonstrated to completely block removal of TG from the plasma and to produce a linear increase in plasma TG levels for at least 90 min. Triton was dissolved in distilled water (300 mg/ml) and injected into tail veins (600 mg/kg) of rats who were under light ether anesthesia. Blood was withdrawn from the tail of conscious rats before and at 45 and 90 min after the injection. The rate was calculated from the increment of plasma TG values per minute multiplied by plasma volume of rats and expressed as μmol/min.

VLDL-TG clearance. The half-life ($t_{1/2}$) of VLDL endogenously radiolabeled with [2-^{3}H]glycerol was monitored as previously described (19). We injected 100 μCi of [2-^{3}H]glycerol into the tail vein of donor rats who were under light ether anesthesia. Blood was obtained 40 min later from the abdominal aorta (with EDTA) while rats were under pentobarbital anesthesia. Endogenously labeled VLDL was obtained from plasma by ultracentrifugation using a Beckman 50Ti rotor at 39,000 rpm and 4°C for 16 h. VLDL was collected by slicing the centrifuge tube and served for monitoring the $t_{1/2}$. Radiolabeled VLDL was injected into recipient animals who were under pentobarbital anesthesia. The mass of TG injected was never >10% of the recipient's total plasma TG pool. [^{3}H]VLDL from one donor rat was injected into no more than two recipients. Blood samples (0.45 ml) were drawn from an indwelling polyethylene cannula (PE-50, I.D. 0.58 mm) in the opposite femoral vein at 2, 4, 6, 8, and 10 min after the injection of radiolabeled VLDL. After each blood sampling, the cannula was flushed with 0.15 ml of 0.9% NaCl. Radiolabeled TG was extracted from 0.2 ml of plasma with 4.8 ml of isopropyl alcohol in the presence of 2 g of heat-reactive zeolite (Sigma, St. Louis, MO). Preliminary investigations showed that, under these conditions, >97% of the label in the isopropyl alcohol was in TG. The solvent extract, 2.5 ml, was then dried under nitrogen, and radioactivity was counted in ACS-2 (Amersham, Tokyo, Japan), using an Aloka LSC-903 (Aloka, Tokyo, Japan) liquid scintillation counter, with autoquench correction. The decline in plasma TG radioactivity ($t_{1/2}$) was used as a measure of the rate of catabolism. We have previously discussed the validity of this TG kinetic model in detail (19). Essentially, the decline in plasma radioactivity after injection of labeled VLDL was monoexponential ($r > 0.95$) under steady state in all VLDL-TG turnover studies. Therefore, $t_{1/2}$ was directly determined by a least-squares linear regression analysis (20). A steady-state condition of TG was assumed if plasma TG concentration 10 min posttracer injection was within 10% of preinjection concentration. Our VLDL preparation may have contained some chylomicrons and their remnants. However, kinetic studies would not have been affected by their presence, because under these conditions <10% of the label is incorporated into intestinal lipoprotein lipids (21). Therefore, the VLDL-TG kinetic data are not significantly affected by the presence of chylomicrons (22).

Plasma lipoprotein lipase (LPL) and hepatic lipase (HL). Postheparin LPL and HL activity were determined by a modification of the method of Nakai et al. (23). Food was removed 3 h before measurement. The rats, while under pentobarbital anesthesia, were injected with 1,000 U/kg heparin. Blood samples were obtained 10 min later from the jugular vein. Plasma was separated by centrifugation at 4°C, and lipase activities were determined immediately. In preliminary studies, lipase activities reached a maximum at 2 min, and the highest activities were maintained for 30 min. A TG emulsion was used as a substrate and radiolabeled oleic acid liberated as a result of the hydrolysis was extracted as described by Belfrage and Vanghan (24). Lipase activity was calculated according to Nilsson-Ehle and Schotz (25). One unit of lipolytic activity was defined as 1 μmol of fatty acid released per milliliter plasma per hour.

Assays. All blood samples were centrifuged at 4°C, and plasma was stored at −20°C until assayed. Plasma glucose, TG, and cholesterol were determined enzymatically using Encore (Baker Instruments, Allentown, PA). Plasma insulin and NEFA were measured using a commercial kit (Shionoria, Shionogi, Osaka, and Iatron Laboratories, Tokyo, Japan).

Data are expressed as means ± SE. Statistical significance was assessed by Duncan's multiple range test (26).

RESULTS

Although lean and fatty control rats did not gain weight, fructose-fed rats receiving pioglitazone gained more than fructose-fed rats receiving no pioglitazone (Table 1). There-

TABLE 2
Changes in postprandial plasma levels of glucose and insulin in response to fructose feeding alone or in combination with pioglitazone in Wistar fatty rats

	Time (weeks)			
	0	1	2	3
Glucose (mmol/l)				
Lean controls	7.0 ± 0.1*	6.7 ± 0.1*	6.6 ± 0.1*	6.8 ± 0.2*
Fatty controls	17.6 ± 0.7†	18.0 ± 0.7†	18.2 ± 0.4†	17.7 ± 1.5†
Fructose-fed fatty rats	18.0 ± 0.5†	18.0 ± 0.8†	19.0 ± 0.9†	19.5 ± 1.2†
Fructose- and pioglitazone-fed fatty rats	16.7 ± 1.0†	7.4 ± 0.4*	6.4 ± 0.3*	7.8 ± 0.4*
Insulin (pmol/l)				
Lean controls	666 ± 84*	516 ± 36*	474 ± 36*	468 ± 30*
Fatty controls	6,420 ± 1,128†	7,296 ± 672†	7,398 ± 966†	8,484 ± 666†
Fructose-fed fatty rats	6,624 ± 618†	7,248 ± 522†	7,776 ± 672†	7,428 ± 402†
Fructose- and pioglitazone-fed fatty rats	7,614 ± 780†	3,252 ± 588§	2,226 ± 294§	2,346 ± 390§

Data are means ± SE of 11 rats in each group. Groups of rats and their designations are the same as in Table 1. Means at the same time periods not sharing a common symbol are significantly different at $P < 0.05$ or less.

TABLE 3
Time-course changes in postprandial plasma concentrations of TG, cholesterol, and NEFA in Wistar fatty rats

Time (weeks)	0	1	2	3
TG (mmol/l)				
Lean controls	0.82 ± 0.06*	0.72 ± 0.05*	0.69 ± 0.06*	0.69 ± 0.03*
Fatty controls	3.62 ± 0.26†	3.90 ± 0.23†	4.08 ± 0.29†	3.94 ± 0.34†
Fructose-fed fatty rats	3.97 ± 0.25†	6.66 ± 0.64§	7.63 ± 0.59§	7.29 ± 0.76§
Fructose- and pioglitazone-fed fatty rats	3.85 ± 0.24†	1.20 ± 0.11*	1.39 ± 0.09*	1.26 ± 0.05*
Cholesterol (mmol/l)				
Lean controls	2.48 ± 0.03*	2.40 ± 0.05*	2.51 ± 0.05*	2.12 ± 0.05*
Fatty controls	4.06 ± 0.10†	3.96 ± 0.10†	4.37 ± 0.13†	4.40 ± 0.13†
Fructose-fed fatty rats	4.06 ± 0.16†	4.94 ± 0.13§	5.28 ± 0.18§	4.84 ± 0.16§
Fructose- and pioglitazone-fed fatty rats	4.22 ± 0.16†	4.19 ± 0.10†	3.83 ± 0.16‡	3.36 ± 0.10‡
NEFA (μmol/l)				
Lean controls	265 ± 106*	326 ± 138*	372 ± 196*	230 ± 46*
Fatty controls	240 ± 13*	337 ± 56*	403 ± 112*	391 ± 52†
Fructose-fed fatty rats	302 ± 62*†	396 ± 47*	433 ± 71*	491 ± 84†
Fructose- and pioglitazone-fed fatty rats	355 ± 57†	245 ± 198*	294 ± 124*	480 ± 224†

Data are means ± SE of 11 rats for TG and cholesterol and 6 rats for NEFA in each group. Groups of rats and their designations are the same as in Table 1. Means at the same time periods not sharing a common symbol are significantly different at $P < 0.05$ or less.

fore, the former group of rats weighed more than the latter. This is due to a greater caloric intake from rat food, but not from fructose, in pioglitazone-treated rats.

As previously reported (16,27), Wistar fatty rats were characterized by hyperglycemia, hyperinsulinemia, and hyperlipidemia (Tables 2 and 3). Although feeding fructose into fatty rats did not change plasma levels of glucose and insulin (Table 2), it doubled postprandial TG concentrations (Table 3). This was evident even 1 week after the start of fructose feeding. Pioglitazone treatment in fructose-fed fatty rats completely prevented the development of hypertriglyceridemia and substantially lowered postprandial plasma levels not only of TG (Table 3) but also of glucose (Table 2) to the value in lean controls. These were evident at 1 week after the start of pioglitazone treatment and continued throughout the study. In addition, a decrease in insulin levels was found in fructose-fed fatty rats receiving pioglitazone (Table 2). However, their concentrations were still greater than lean controls.

A sixfold elevation of fasting TG concentrations in fatty control subjects compared with lean control subjects was associated with a threefold increase in the production rate of TG (Fig. 1). In addition, the half-life of VLDL-TG isolated from lean donors was longer by 285% in fatty control recipients than in lean control recipients (Fig. 2). Furthermore, the half-life of VLDL-TG from fatty control donors was longer by 53% in lean recipients than that from lean control donors (Fig. 3). However, there was no difference in the activity of LPL and HL between the two groups (Fig. 4).

A fructose-induced increase by 86% in TG concentrations in fatty rats was associated with a further increase in TG secretion by 56% (Fig. 1). However, there was no significant differences between fatty recipients with and without fructose supplementation in the half-life of VLDL-TG from lean donors (Fig. 2), although the mean half-life was somewhat longer in fructose-fed fatty rats than in fatty rats fed food only. In addition, in lean control recipients, the half-life of VLDL-TG from fructose-fed fatty donors was similar to that from fatty donors receiving no fructose supplementation (Fig. 3). The activity of LPL in postheparin plasma was greater in fructose-fed fatty rats than in fatty control rats, whereas no difference was found in the activity of HL between the two groups.

Pioglitazone treatment in fructose-fed fatty rats produced a fall in fasting levels of TG, from 6.36 ± 0.64 to 2.24 ± 0.10 mmol/l (Fig. 1), though these are still greater compared with the concentrations in lean rats (0.59 ± 0.02 mmol/l). This was not

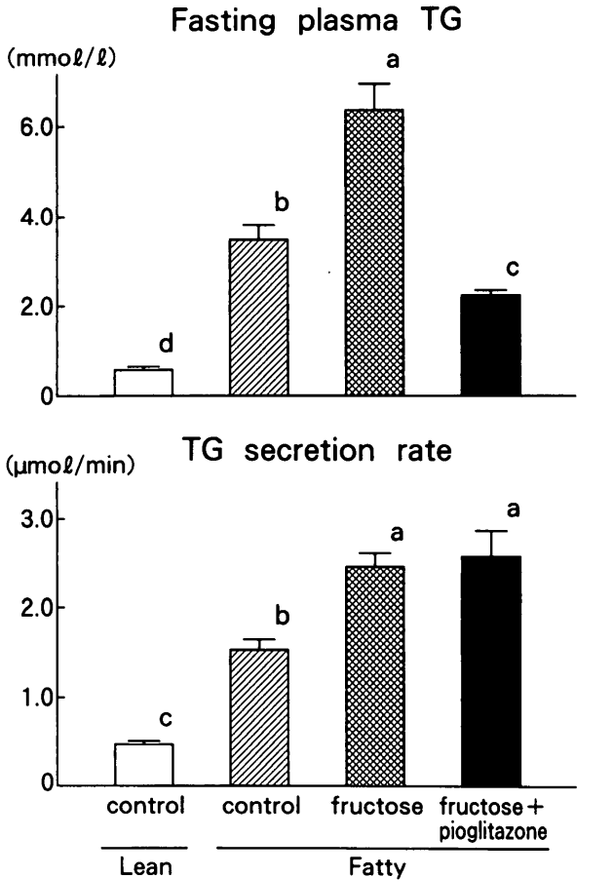

FIG. 1. Fasting plasma TG concentrations and TG secretion rates measured at the end of 3 weeks of fructose feeding alone or in combination with pioglitazone. Fructose was supplied as a 10% drinking solution, and pioglitazone (3 mg/kg body weight, suspended in 0.5% methyl cellulose) was given daily through a gastric tube into the stomach. Both fructose and pioglitazone were given for 3 weeks. Data are means ± SE of five rats in each group. Groups of rats are the same as in Table 1. Means not sharing common letters are significantly different from each other at $P < 0.05$ or less.

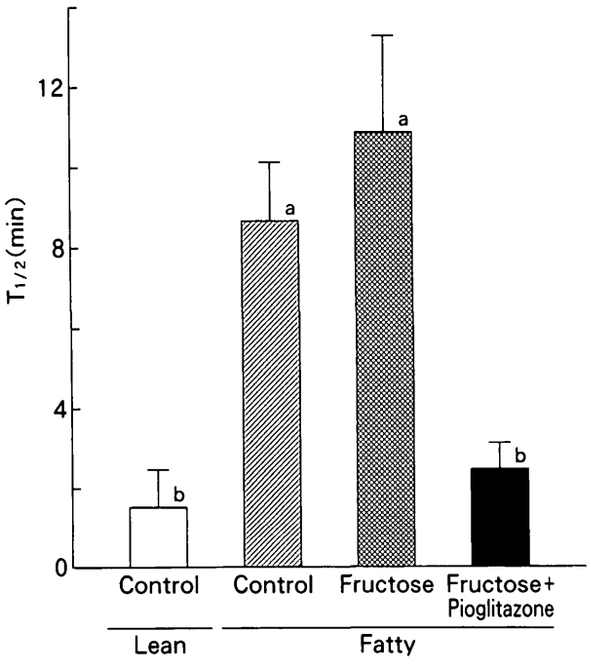

FIG. 2. Half-life ($T_{1/2}$) of VLDL-TG isolated from lean donors. VLDL was endogenously radiolabeled with [2-^{3}H]glycerol in lean donor rats fed food only, isolated, and then injected into four groups of recipient animals, three groups of Wistar fatty rats and one group of lean controls. Subsequent decline in plasma radioactivity with time was used to calculate plasma half-life of labeled triglyceride. Data are means ± SE of five rats in each group. Groups of rats are the same as in Table 1. Means not sharing common letters are significantly different from each other at $P < 0.05$ or less.

associated with changes in TG secretion (Fig. 1). However, the half-life of VLDL-TG from lean donors was shorter by 74% in fructose-fed fatty recipients receiving pioglitazone than in fructose-fed fatty recipients receiving no pioglitazone and was almost the same as that in lean recipients (Fig. 2). In contrast, the activity of LPL and HL did not differ in post-heparin plasma between the two groups (Fig. 4). There was no differences in the half-life in lean recipients between VLDL-TG from fructose-fed fatty donors receiving pioglitazone and those receiving no pioglitazone (Fig. 2).

At the end of the experiments, plasma NEFA concentrations were greater in three groups of fatty rats than in lean rats (Table 3). Neither fructose feeding nor pioglitazone treatment produced any significant changes in plasma NEFA levels, although the level in pioglitazone-treated rats was lower than that in the other two groups of fatty rats at weeks 1 and 2. Fractional catabolic rates of TG, calculated using data depicted in Fig. 1, in the four groups of rats were quantitatively identical to the half-life of VLDL-TG from lean donors shown in Fig. 2 (lean control, 0.055 ± 0.005/min; fatty control, 0.025 ± 0.001/min; fructose-fed fatty, 0.020 ± 0.002/min; pioglitazone-treated-fructose-fed fatty, 0.051 ± 0.004/min).

DISCUSSION

The present studies demonstrate hypersecretion of TG-rich lipoproteins by livers of Wistar fatty rats. This may be associated with obesity, hyperphagia, and hyperinsulinemia in Wistar fatty rats. TG secretion rates averaged 16.2 ± 0.1 μmol/min in fatty rats receiving no fructose feeding, and this figure was comparable to the rate of secretion obtained by the Triton method in Zucker fatty rats (7). Although TG production rates would be underestimated in the Triton method (28), it is nevertheless reproducible and reliable when it is used for comparisons between different genotypes or diets. In addition to overproduction of TG-rich lipoproteins, Wistar fatty rats fed food only cleared VLDL-TG isolated from lean donors less effectively than did lean rats, although there was no difference in LPL activity in post-heparin plasma between lean and fatty rats. Furthermore, lean rats cleared VLDL-TG isolated from fatty rats less effectively than VLDL-TG from lean rats. Taken together, it is concluded that hypertriglyceridemia found in Wistar fatty rats is associated with hepatic overproduction and defects in catabolism of TG-rich lipoproteins, the latter is accompanied not only by an impairment in the ability of fatty rats to remove VLDL-TG from the circulation but also by changes in the nature of VLDL particles to be cleared. Mechanisms by which defects in VLDL-TG catabolism resulted are unknown.

In the present study, feeding fructose into Wistar fatty rats produced an 86% elevation in TG concentrations. This was associated with a 56% increase in TG production rates. However, there were no differences in the half-life studied in lean recipients between VLDL-TG from Wistar fatty donors with and without fructose supplementation, suggesting that fructose-feeding for 21 days had little effect on the properties of VLDL particles in Wistar fatty rats to be cleared in lean normal control rats. In contrast, the half-life of VLDL-TG from lean donors tended to be longer in fructose-fed fatty rats than in fatty rats receiving no fructose. This occurred despite the larger mean plasma TG pool in fructose-fed fatty rats. In addition, LPL activity in posthepalin plasma in fructose-fed fatty rats was higher than that in fatty rats receiving no fructose but was comparable to that in lean rats. Removal of plasma TG depends on the activities of endothe-

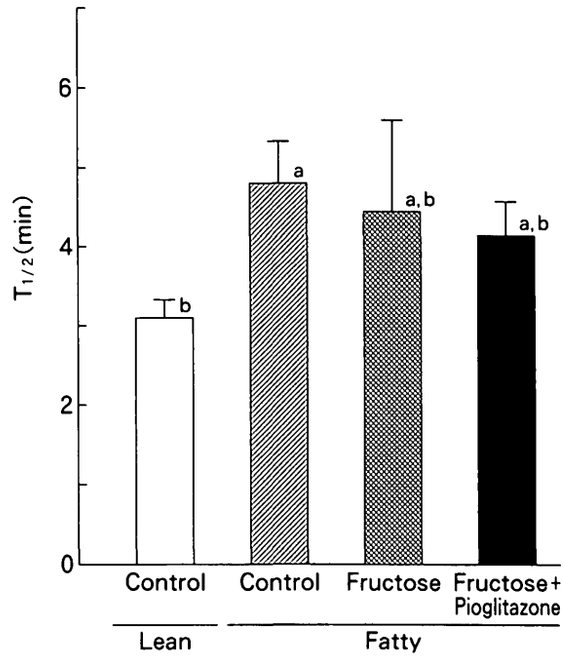

FIG. 3. Half-life ($T_{1/2}$) of VLDL-TG measured in lean recipients. VLDL was endogenously radiolabeled in four groups of donor rats and then injected into lean recipients. Half-life of labeled TG was calculated from a subsequent decline in plasma radioactivity. Data are means ± SE of five rats in each group. Groups of rats are the same as in Fig. 1. Means not sharing common letters are significantly different from each other at $P < 0.05$ or less.

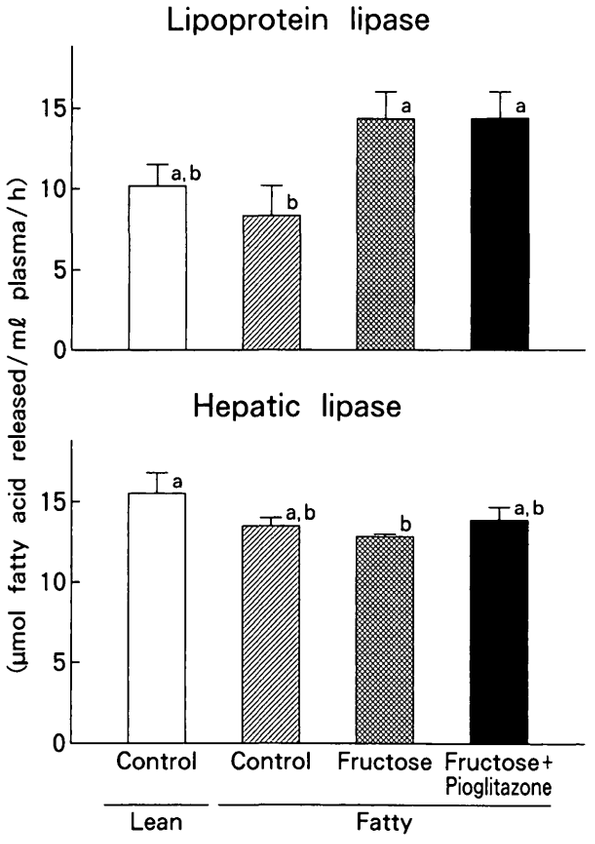

FIG. 4. Postheparin plasma lipase activities in three groups of Wistar fatty rats and one group of lean controls. Data are means ± SE of five rats in each group. Groups of rats are the same as in Fig. 1. Means not sharing common letters are significantly different from each other at $P < 0.05$ or less.

lial lipases, particularly LPL (29) and on the ability of the liver to remove VLDL-TG. Taken together, we conclude that a fructose-induced increase in plasma TG in Wistar fatty rats may be explained in part by an impairment in the ability of their livers to remove VLDL-TG, as previously reported in Wistar lean rats (9), in addition to a further increase in the production rates of VLDL-TG by their livers.

Pioglitazone reduced plasma glucose, insulin, and TG levels in Wistar fatty rats who were fed fructose, as previously reported in Wistar fatty rats (12,27,30) and in animals with insulin resistance (10,15,31). Pioglitazone has been reported to increase insulin sensitivity by activating insulin receptor kinase in Wistar fatty rats (12), through which it decreased plasma glucose and insulin levels. The substantial fall observed in fructose-fed fatty rats in plasma TG concentrations with pioglitazone treatment, in the absence of reductions of TG production, suggests that pioglitazone ameliorates defects in catabolism of VLDL-TG. Indeed, fructose-fed fatty rats receiving pioglitazone were found to clear VLDL-TG from lean donors at a much faster rate compared with fructose-fed fatty rats receiving no pioglitazone and at a similar rate to lean controls. This could be true because of the larger plasma TG pool, which was reported to reduce efficiency of TG removal (32), in fructose-fed Wistar fatty rats receiving pioglitazone compared with lean control. This occurred despite no increase in LPL activity with pioglitazone in postheparin plasma. In addition, lean recipients cleared VLDL-TG obtained from fructose-fed fatty rats receiving pioglitazone at a similar rate as VLDL-TG obtained from fructose-fed fatty rats receiving no pioglitazone. These results have shown that pioglitazone ameliorates an impairment of Wistar fatty rats fed fructose to remove VLDL-TG, thereby contributing to a fall in an increased TG concentration, although the mechanisms by which this resulted are unknown.

In conclusion, we have demonstrated that hypertriglyceridemia found in Wistar fatty rats, an animal model of NIDDM, is attributed to an increased TG production as well as impaired TG removal, the latter is due to both changes in VLDL, such that they are less able to be removed, and changes in the nature of Wistar fatty rats, such that they are less able to remove VLDL-TG. Fructose feeding further increases hepatic TG production with a resultant deterioration in hypertriglyceridemia. Pioglitazone ameliorates glycemia and triglyceridemia to the level of lean control rats and insulinemia to a lesser extent. Pioglitazone alters the physiology of the Wistar fatty rats fed fructose in a manner that increases their ability to remove VLDL-TG from the circulation. However, it produces no change in TG overproduction, the nature of VLDL-TG to be cleared, and activities of postheparin LPL and HL. Although precise mechanisms through which pioglitazone ameliorates an impairment in the ability of fructose-fed Wistar fatty rats to remove VLDL-TG at present remain unknown, they may be associated with an improvement in insulin resistance in these rats.

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