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Triglyceride-lowering effect of a novel insulin-sensitizing agent, JTT-501

Tsutomu Shibata *, Kenichi Matsui, Fumihiko Yonemori, Korekiyo Wakitani

Central Pharmaceutical Research Institute, Japan Tobacco, 1-1, Murasaki-cho, Takatsuki, Osaka 569-1125, Japan

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Abstract

JTT-501, 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3, 5-isoxazolidinedione, is a novel insulin-sensitizing agent. We investigated the triglyceride-lowering activity of JTT-501 in a high-fat (HF) rat model. The HF rats showed insulin resistance with elevation of fasting insulin levels and reduction of insulin-stimulated glucose oxidation. There was also a tendency towards increased basal insulin and triglyceride levels. Oral administration of JTT-501 (3–30 mg kg^{-1} day^{-1} for 7 days) reduced basal triglyceride levels dose dependently with a minimum effective dose of 3 mg kg^{-1} day^{-1}. Furthermore, regarding triglyceride metabolism, JTT-501 (30 mg kg^{-1} day^{-1} for 15 days, p.o.) decreased hepatic triglyceride output rate and serum triglyceride half-life ($T_{1/2}$). In contrast, pioglitazone (30 mg kg^{-1} day^{-1} for 15 days, p.o.) reduced $T_{1/2}$, but did not affect hepatic triglyceride output rate. We conclude that JTT-501 possesses potent triglyceride-lowering activity due to its inhibition of triglyceride secretion from the liver and enhancement of triglyceride disposal in peripheral tissues.

Keywords: Insulin-sensitizing agent; JTT-501; Triglyceride

1. Introduction

Hypertriglyceridemia is the most frequent form of hyperlipidemia observed in type 2 diabetes, because it co-exists with hyperinsulinemia in the general population (Steiner and Lewis, 1996). Insulin regulates triglyceride metabolism through up-regulation of triglyceride synthesis, but decreases secretion of triglyceride-rich lipoprotein, very low density lipoprotein (VLDL), from the liver (Sparks and Sparks, 1994; Steiner and Lewis, 1996) and enhances triglyceride disposal mediated by activation of lipoprotein lipase in peripheral tissues (Sadur and Eckel, 1982). However, in insulin-resistant type 2 diabetes, hyperinsulinemia leads to an increase in triglyceride synthesis and secretion of VLDL (Sparks and Sparks, 1994; Steiner and Lewis, 1996) and a decrease in lipoprotein lipase activity (Eckel, 1989). Attention has recently focused on the thiazolidinediones that enhance insulin sensitivity in peripheral tissues (Saltiel and Olefsky, 1996). We have developed a novel insulin-sensitizing agent, JTT-501, 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione, which is structurally distinct from the thiazolidinediones (Shinkai et al., 1998). We have previously clarified that JTT-501 possesses not only anti-diabetic activity but also a triglyceride-lowering activity which is more potent than that of pioglitazone and of troglitazone (Shibata et al., 1999). Regarding regulation of triglyceride metabolism by pioglitazone, this agent elevates the disposal rate of triglyceride in peripheral tissues without affecting hepatic triglyceride output (Sugiyama et al., 1990). Accordingly, we performed the present study to clarify which of the target sites, liver and peripheral tissues, are influenced by JTT-501 regarding triglyceride metabolism, using a high-fat (HF) rat model.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats were purchased from Charles River Japan (Tokyo, Japan) and Keari (Osaka, Japan).

* Corresponding author. Tel.: +81-726-81-9700; Fax: +81-726-81-9722

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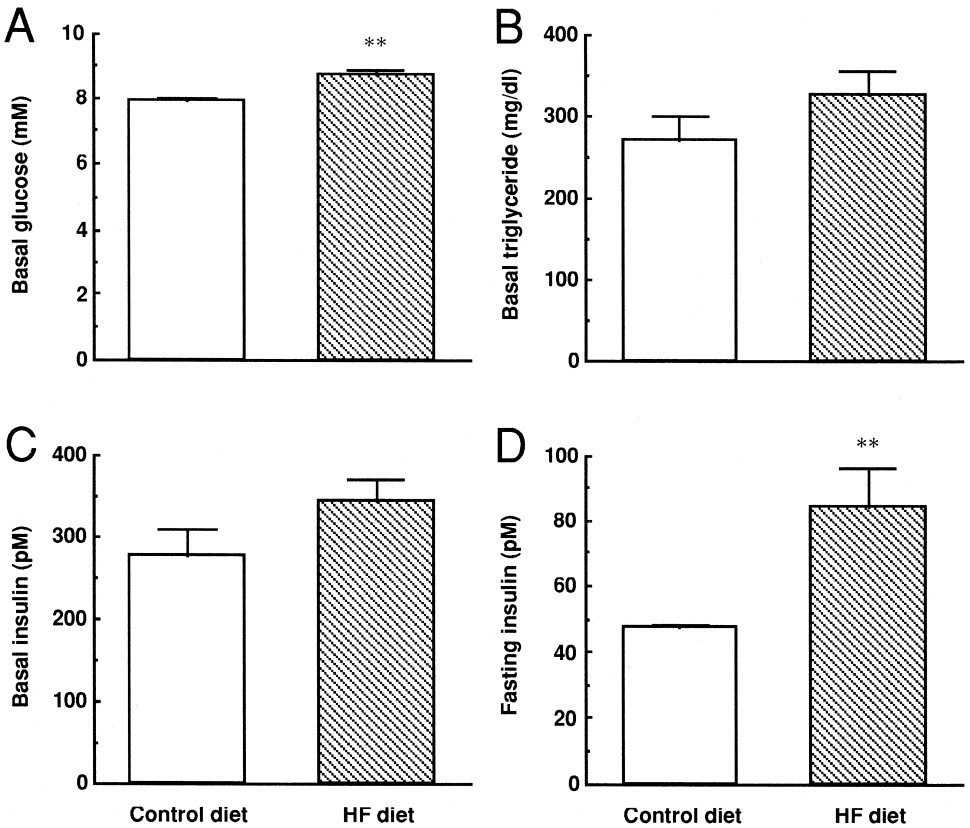

Fig. 1. Effects of HF diet on serum glucose, triglyceride and insulin levels. Male Sprague–Dawley rats (5 weeks old) received control diet or HF diet for 2 weeks. Blood samples were taken from the tail vein of fed or fasted rats. Basal glucose (A), insulin (B), triglyceride (C), and fasting insulin (D) were measured. Each column represents the mean ± S.E.M. (panel A–C, $n = 10$; panel D, $n = 5$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control diet group (Student's *t*-test).

The animals were maintained on a standard laboratory chow diet (3.6 kcal g^{-1}, protein 23.1%, carbohydrate 53.5%, fat 5.9%, Oriental Yeast, Tokyo, Japan), and water ad libitum. To induce insulin resistance, Sprague–Dawley rats were fed a HF diet (5.0 kcal g^{-1}, protein 24.5%, carbohydrate 11.5%, and fat 50%, Clea Japan, Tokyo, Japan) for 2–4 weeks. The animals were housed in plastic cages in a room with controlled temperature (25 ± 3°C), humidity (55 ± 15%), and light (0800–2000 h).

2.2. Compounds and administration

JTT-501 and pioglitazone were synthesized at the Central Pharmaceutical Research Institute, Japan Tobacco, (Takatsuki, Osaka, Japan). JTT-501 (3–30 mg kg^{-1} day^{-1}) and pioglitazone (30 mg kg^{-1} day^{-1}) suspended in 0.5% sodium carboxymethylcellulose (CMC-Na, Tokyo Kasei, Tokyo, Japan) solution were administered orally once daily by stomach tube. Matched control rats were given 0.5% CMC-Na solution orally for the same period.

2.3. Analytical methods

The serum glucose and triglyceride concentrations were measured, using commercial kits (Boehringer Mannheim, Tokyo, Japan) by COBAS FARA II (Roche, Tokyo, Japan). The serum insulin concentration was measured with an insulin radioimmunoassay kit (Shionogi, Tokyo, Japan)

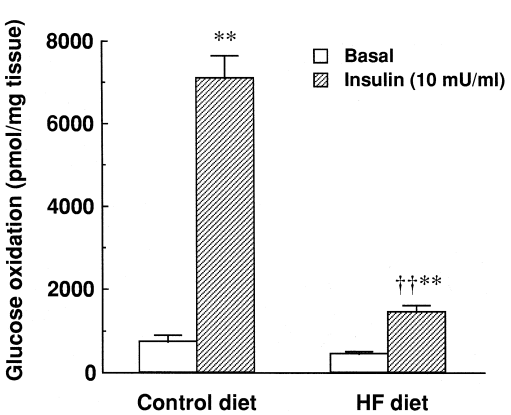

Fig. 2. Effect of HF diet on glucose oxidation in adipose tissues. Male Sprague–Dawley rats (5 weeks old) received control diet or HF diet for 2 weeks. The epididymal fat pads were removed and then chopped samples were incubated in Hanks' balanced salt solution containing glucose (5.6 mM), [(U)-^{14}C]glucose (20.72 kBq ml^{-1}), and insulin (0–100 mU ml^{-1}) for 2 h at 37°C. Synthesized $^{14}CO_2$ was trapped and counted with a scintillation counter. Each column represents the mean ± S.E.M. ($n = 5$). $^{**}P < 0.01$ vs. each basal; ††$P < 0.01$ vs. control diet group (Student's *t*-test).

with rat insulin (Linco Research, St. Charles, MO) as a standard, with an automatic gamma counter 1470 WIZARD™ (Wallac Oy, Turuk, Finland). The minimum detectable concentration was 0.1 ng ml^{-1} in the insulin assay. The intra- and inter-assay variations were less than 5%.

2.4. Measurement of glucose oxidation in adipose tissues

The epididymal fat pads were removed from rats and then chopped samples were incubated in Hanks' balanced salt solution (GIBCO, Grand Island, NY, USA) containing 4% bovine serum albumin (Fraction V, Sigma, St. Louis, MO, USA), 20.72 kBq ml^{-1} [(U)-^{14}C]glucose (New England Nuclear, Boston, MA, USA), and 0–100 mU ml^{-1} insulin from bovine pancreas (Sigma) for 2 h at 37°C. Synthesized $^{14}CO_2$ was trapped with Scintilamine®-OH (Dojindo, Tokyo, Japan) on filter paper and counted with a Liquid Scintillation Analyzer Model 2500 TR (Packard, Meriden, CT, USA). The variation of the glucose oxidation assay was less than 5%.

2.5. Measurement of serum triglyceride disposal and hepatic triglyceride output

We measured triglyceride metabolism as previously described (Sugiyama et al., 1990). Briefly, rats were fasted for 16 h after the last administration of JTT-501 and pioglitazone. Then injection with a lipid emulsion (Intralipos®, 10%, 2 ml kg^{-1}, Midorijuji, Tokyo, Japan) or Triton WR-1339 (20% w/v in saline, 500 mg kg^{-1}, Sigma) into the tail vein was performed to determine the rates of serum triglyceride disposal or hepatic triglyceride output, respectively. Blood samples were taken at 10, 20, and 30 min after the Intralipos® injection, and 0, 30, 60, and 90 min after Triton WR-1339 injection, following which, serum triglyceride concentrations were measured. The rate of serum triglyceride disposal was expressed as half-life time ($T_{1/2}$) of serum levels, and the rate of hepatic triglyceride output as increase in serum concentration per min.

2.6. Statistical analysis

Data are presented as the means ± S.E.M. The significance of differences between two groups was evaluated

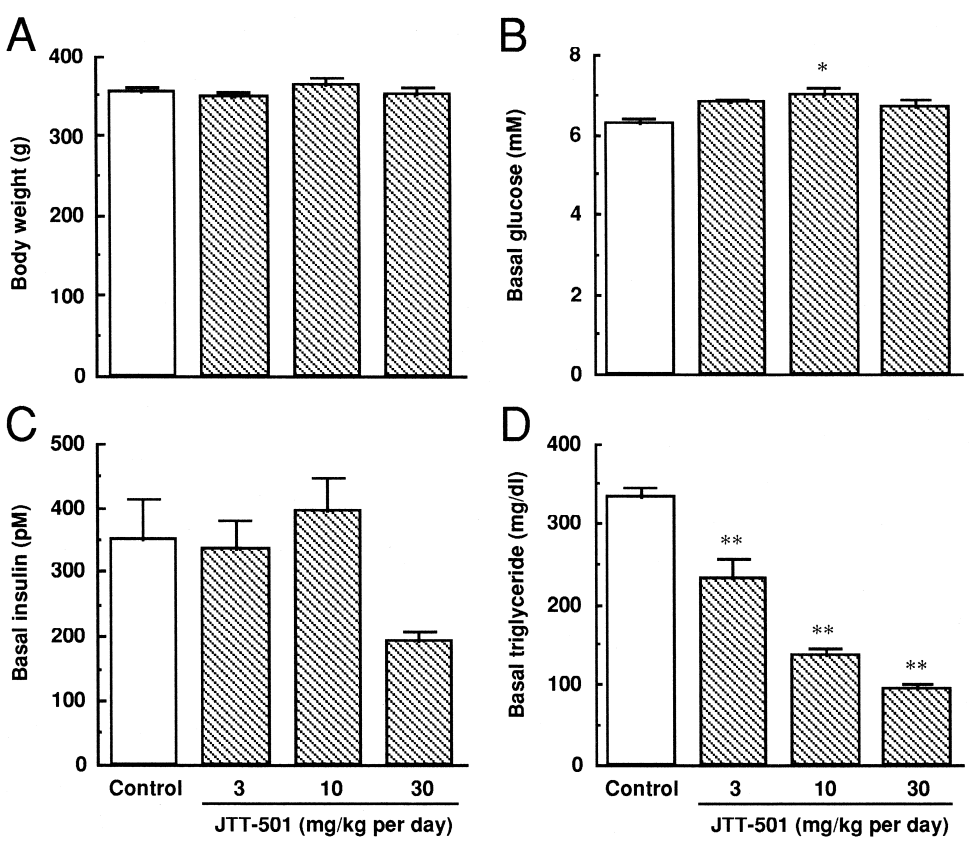

Fig. 3. Effect of JTT-501 on basal glucose, triglyceride and insulin levels in HF rats. Male Sprague–Dawley rats (5 weeks old) received HF diet for 4 weeks. JTT-501 (3–30 mg kg^{-1} day^{-1}) was administered orally for the last 7 days of the diet period. The control group was treated with 0.5% CMC-Na solution during this period. Blood samples were taken from the tail vein of fed rats. Body weight (A), basal glucose (B), insulin (C), and triglyceride (D) were measured. Each column represents the mean ± S.E.M. ($n = 7$). *$P < 0.05$, **$P < 0.01$ vs. control group (ANOVA followed by Dunnett's test).

using Student's *t*-test. For multiple comparisons, one-way analysis of variance (ANOVA) was used. When ANOVA showed significant differences, post-hoc analysis was performed with Dunnett's test or the Tukey's test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Insulin resistance in HF rats

We tested whether HF rats were insulin-resistant. Sprague–Dawley rats were fed a HF diet for 2 weeks. The results are shown in Figs. 1 and 2. Body weights in two groups were not changed (280 ± 5 g for control rats vs. 281 ± 6 g for HF rats, not significant). In HF rats, basal glucose and fasting insulin levels were elevated compared with those in control rats. Basal insulin and triglyceride levels tended to increase in HF rats, but the differences were not significant. Additionally, insulin-stimulated glucose oxidation levels were markedly impaired in adipose tissues from HF rats.

3.2. Effects of JTT-501 on serum parameters in HF rats

We examined whether JTT-501 influences serum parameters in rats receiving a HF diet for 4 weeks. JTT-501 (3, 10, and 30 mg kg^{-1} day^{-1}) was administered orally once daily for the last 7 days of the diet period. The results are shown in Fig. 3. Although JTT-501 did not affect body weight, JTT-501 decreased basal triglyceride levels significantly at doses of 3 mg kg^{-1} day^{-1} or higher. The basal insulin levels tended to decrease at JTT-501 30 mg kg^{-1} day^{-1}, but basal glucose levels were not affected.

3.3. Effects of JTT-501 and pioglitazone on triglyceride metabolism in HF rats

To investigate the differences in effectiveness between JTT-501 and pioglitazone on triglyceride metabolism (hepatic triglyceride output rate and disposal $T_{1/2}$), both compounds (30 mg kg^{-1} day^{-1}) were administered orally to HF rats (HF diet for 6 weeks) once daily for the last 15 days of the diet period. The effects on body weight and serum parameters on day 5 are shown in Fig. 4. The

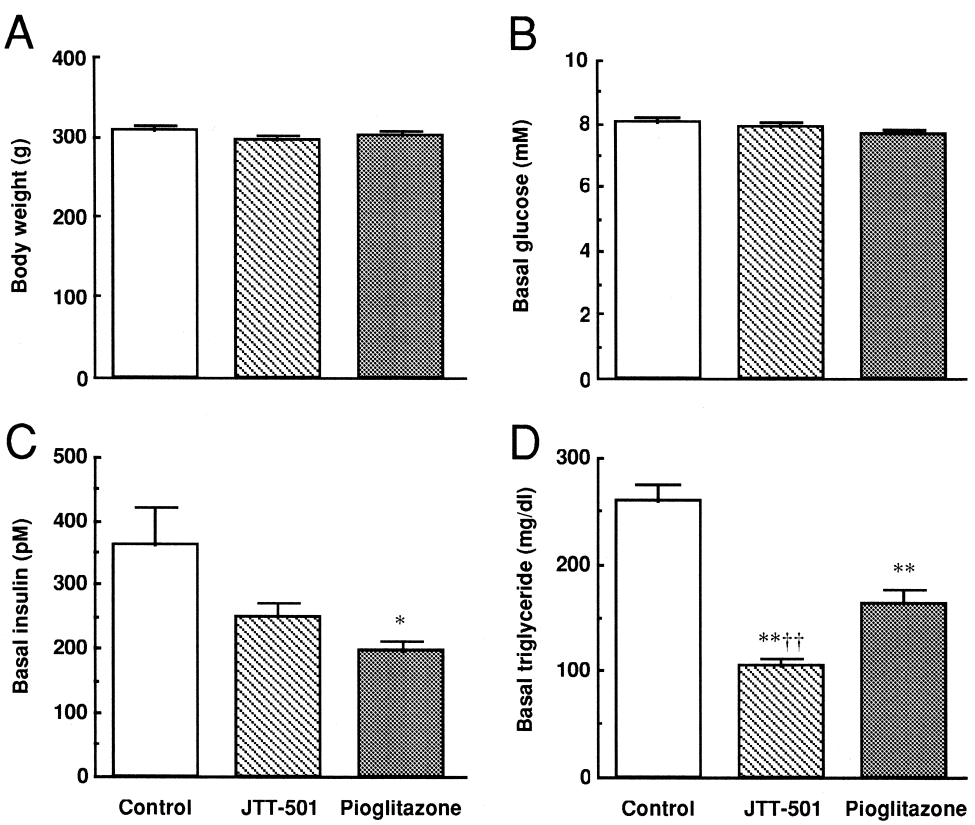

Fig. 4. Effects of JTT-501 and pioglitazone on basal glucose, triglyceride and insulin levels in HF rats. Male Sprague–Dawley rats (6 weeks old) received HF diet for 4 weeks. JTT-501 (30 mg kg^{-1} day^{-1}) and pioglitazone (30 mg kg^{-1} day^{-1}) were administered orally for the last 15 days of the diet period. The control group was treated with 0.5% CMC-Na solution for this period. Blood samples were taken from the tail vein of fed rats on day 5. Body weight (A), basal glucose (B), insulin (C), and triglyceride (D) were measured. Each column represents the mean ± S.E.M. ($n = 10$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control group; $\dagger\dagger P < 0.01$ vs. pioglitazone group (ANOVA followed by the Tukey's test).

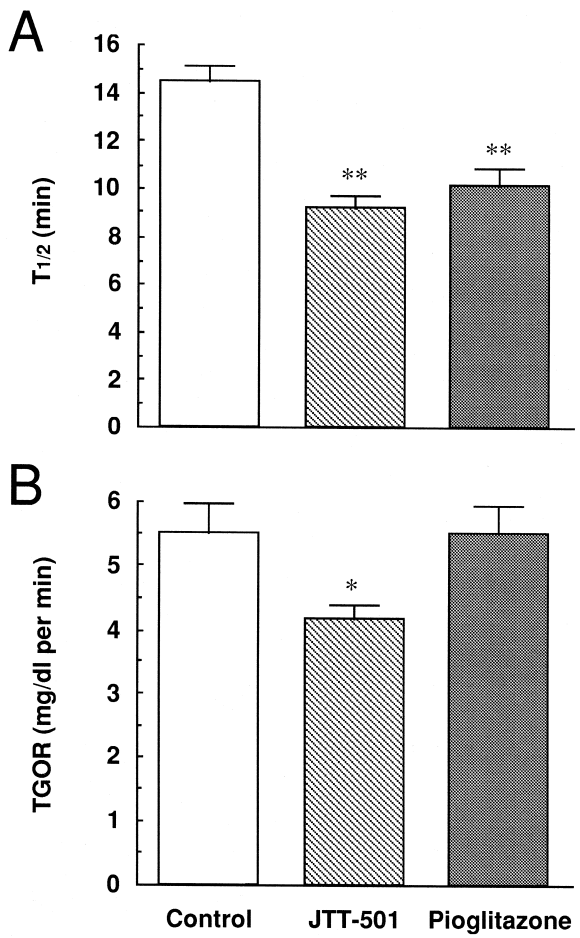

Fig. 5. Effects of JTT-501 and pioglitazone on triglyceride metabolism in HF rats. Rats were fasted for 16 h after the last administration. Injections with Intralipos® or Triton WR-1339 into the tail vein were performed to determine the rates of serum triglyceride disposal (A) or hepatic triglyceride output (B), respectively. Each column represents the mean ± S.E.M. (panel A, $n = 4–5$; panel B, $n = 5$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control group (ANOVA followed by the Tukey's test).

triglyceride-lowering effect of JTT-501 was more potent than that of pioglitazone. Pioglitazone reduced the basal insulin levels while JTT-501 tended to reduce them. In addition, neither compound affected basal glucose levels. The effects on triglyceride metabolism are shown in Fig. 5. JTT-501 and pioglitazone shortened the $T_{1/2}$ of Intralipos® in serum. JTT-501 decreased hepatic triglyceride output rate following injection of Triton WR-1339, but pioglitazone did not.

4. Discussion

To evaluate its triglyceride-lowering effect, we investigated the effect of the insulin-sensitizing agent, JTT-501, on hepatic triglyceride output rate and triglyceride disposal in peripheral tissues, and compared them with the effects of pioglitazone. In the present study, we demonstrated that JTT-501 possesses potent triglyceride-lowering activity mediated by the inhibition of triglyceride secretion from liver and the enhancement of triglyceride disposal in peripheral tissues.

Since insulin-resistant type 2 diabetes involves metabolism abnormalities, not only of glucose, but also of lipids, the development of a therapy for hyperlipidemia is an important goal. We have previously demonstrated that JTT-501 improves abnormal serum glucose, insulin and triglycerides, and enhances insulin action in insulin-resistant rodents such as KK-A^{y} mice, or Zucker diabetic fatty rats (Shibata et al., 1999). Furthermore, JTT-501 decreases serum triglyceride levels more potently than does either troglitazone or pioglitazone. This triglyceride-lowering effect is also seen in male and female normal rats.

It is well-known that an HF diet influences insulin action and causes insulin resistance (Storlien et al., 1996; Shibata et al., 1998). Previous reports indicate that the HF rat model exhibits insulin resistance with hypertriglyceridemia (Maegawa et al., 1986; Iwanishi and Kobayashi, 1993). Our HF rats obviously had both insulin resistance with hyperinsulinemia in the fasting state and impaired insulin-stimulated glucose oxidation, and showed hyperglycemia and a tendency to hypertriglyceridemia and hyperinsulinemia in the basal state. JTT-501 decreased serum triglyceride levels in a dose-dependent manner. The minimum effective dose was less than 3 mg kg^{-1} day^{-1}, p.o. JTT-501 shortened the $T_{1/2}$ of triglyceride in serum and decreased hepatic triglyceride output rate, indicating that JTT-501 accelerates the disposal of exogenous triglyceride in peripheral tissues and reduces triglyceride secretion from the liver, respectively. These results suggest that JTT-501 decreases serum triglyceride levels by increasing triglyceride disposal and decreasing hepatic triglyceride output. On the other hand, pioglitazone enhanced triglyceride disposal in peripheral tissues but did not affect the hepatic triglyceride output, a result which is identical with the previous report (Sugiyama et al., 1990).

In peripheral tissues, insulin increases triglyceride disposal through activation of lipoprotein lipase (Sadur and Eckel, 1982). However, in diabetes, there is typically a decrease of lipoprotein lipase activity (Eckel, 1989; Abbate and Brunzell, 1990). In particular, insulin resistance leads to 30–60% decreases of lipoprotein lipase activity in type 2 diabetes patients (Pfeifer et al., 1983; Knudsen et al., 1995; Yost et al., 1995) and of about 60% in the insulin-resistant rodent model (Yamazaki et al., 1997). It is therefore thought that the stimulating effect of JTT-501 on triglyceride disposal is associated with lipoprotein lipase activity, a possibility consistent with previous findings (Yamazaki et al., 1997). Moreover it has been established that activation of the nuclear PPAγ receptor is associated with lipoprotein lipase expression (Robinson et al., 1998), and that JTT-501 activates the PPAγ receptor as do thiazolidinediones (Shibata et al., 1999). We thus speculate that the triglyceride disposal stimulated by JTT-501 is due to a

lipoprotein lipase activity enhanced by PPARγ receptor activation.

In the liver, insulin reduces VLDL secretion while increasing triglyceride synthesis (Sparks and Sparks, 1994; Steiner and Lewis, 1996). However, the hyperinsulinemia as seen in insulin-resistant type 2 diabetes leads to an increase in both triglyceride synthesis and secretion of VLDL (Sparks and Sparks, 1994; Steiner and Lewis, 1996). Our findings of a hepatic triglyceride output rate decreased by JTT-501 indicate a lowered secretion of VLDL from the liver, and we consider that this effect of JTT-501 was associated with a triglyceride-lowering greater than that with pioglitazone. In this study, we did not investigate hepatic triglyceride stores. However, JTT-501 had not influenced liver lipid levels in our preliminary studies (unpublished data).

Furthermore, this effect in the liver leads to speculation that the target of JTT-501 is in the liver. It is known that a nuclear receptor, the PPARα receptor, is specifically expressed in the liver (Braissant et al., 1996) and regulates lipid metabolism (Keller et al., 1993; Schoonjans et al., 1996; Desvergne et al., 1998). We previously reported that pioglitazone and JTT-501 activate the PPARγ receptor with similar potency and efficacy, but that JTT-501 activates the PPARα receptor to a greater extent (Shibata et al., 1999). The difference between JTT-501 and pioglitazone regarding this aspect of triglyceride metabolism is certainly clarified by this difference in PPARα receptor activation. Considering not only the insulin resistance but also the abnormalities of lipid metabolism seen in insulin-resistant type 2 diabetes, we expect that JTT-501, that activates both PPARγ receptor and PPARα receptor, may be a highly suitable therapeutic agent compared with troglitazone and pioglitazone.

Moreover JTT-501 produces not only chronic activation (Shibata et al., 1998; Terasaki et al., 1998) but also acute activation of insulin signal transduction (Maegawa et al., 1999). This acute action is associated with lipid metabolism. Indeed, we found that JTT-501 decreases serum triglyceride levels at 24 h after oral single administration (unpublished data). These results thus suggest that JTT-501 acts via more targets than only PPA receptors. Targets involved in triglyceride metabolism could be lipogenic enzymes, tumor necrosis factor α, or microsomal triglyceride transfer protein. Because the activity of lipogenic enzymes is increased in the type 2 diabetes rodent model (Iritani et al., 1995), tumor necrosis factor α induces hypertriglyceridemia (Feingold and Grunfeld, 1992), and microsomal triglyceride transfer protein is related to triglyceride absorption via the intestine (Gordon et al., 1995). To clarify the effect of JTT-501 on these targets should be a topic for future work.

We conclude that JTT-501 decreases serum triglyceride levels in the insulin-resistant rat model, and that this effect is mediated not only by increasing triglyceride disposal in peripheral tissues but also by decreasing triglyceride output from the liver. It is therefore expected that JTT-501 may be effective against lipid abnormalities in patients with type 2 diabetes.

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