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Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolidinedione derivative

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Abstract

JTT-501, 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione, is an isoxazolidinedione derivative which is structurally distinct from thiazolidinediones such as pioglitazone and troglitazone. We investigated the effects of JTT-501 on insulin-sensitizing activity and in rodent diabetic models. JTT-501 enhanced insulin-stimulated cell differentiation of 3T3-L1 fibroblasts with an EC_{50} value of 110 nM. Furthermore, JTT-501 activated peroxisome proliferator-activated (PPA) $_{\gamma}$ and $_{\alpha}$ receptors with the $EC_{5\text{-fold}}$ values of 0.28 and 5.4 μM, respectively. In the non-insulin-dependent diabetes mellitus model KK-A^{y} mice, JTT-501 improved hyperglycemia, hyperinsulinemia and hypertriglyceridemia, and enhanced insulin-stimulated glucose oxidation in adipose tissues. JTT-501 was also effective in the non-insulin-dependent diabetes mellitus model Zucker diabetic fatty (ZDF) rats but not in the insulin-dependent diabetes mellitus model streptozotocin-induced diabetic mice. These observations suggest that JTT-501 enhances insulin sensitivity in peripheral tissues and improves hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in non-insulin dependent diabetes mellitus models. In particular, the triglyceride-lowering activity of JTT-501 is a unique characteristic compared to the thiazolidinediones. Therefore, JTT-501 may be a promising antidiabetic agent for treating non-insulin-dependent diabetes mellitus patients with insulin resistance.

Keywords: JTT-501; Isoxazolidinedione; Antidiabetic agent; Non-insulin-dependent diabetes mellitus; Insulin resistance; PPA (peroxisome proliferator-activated) receptor

1. Introduction

Hyperglycemia in non-insulin-dependent diabetes mellitus patients is a result of both impaired insulin secretion in pancreatic β-cells and insulin resistance in peripheral tissues. The sulfonylureas have been widely used as oral antidiabetic agents, which enhance insulin secretion in pancreatic β-cells (Zimmerman, 1997). However, sulfonylureas sometimes induce severe and prolonged hypoglycemia, and chronic administration occasionally impairs their effectiveness (Burge et al., 1998). In addition, they are not necessarily suitable for treating non-insulin-dependent diabetes mellitus patients with obesity and insulin resistance (Campbell, 1990). Many patients who have hyperinsulinemia release sufficient insulin but the insulin utilization is down-regulated, and thus sulfonylureas are not effective in these patients. Therefore, non-insulin-dependent diabetes mellitus patients with insulin resistance in skeletal muscle, adipose tissues, and liver create a need to develop effective drugs that enhance insulin sensitivity at these sites. It is thought that the need to develop such drugs is made even more important by the fact that insulin resistance may play a role in the etiology of a wider spectrum of metabolic disorders such as obesity, hypertension, and atherosclerosis (Reaven, 1988; DeFronzo and Ferrannini, 1991).

Recently, attention has focused on insulin sensitizers, a new class of oral antidiabetic agents, for insulin-resistant patients, and in particular on the thiazolidinediones including troglitazone (Fujiwara et al., 1988) and pioglitazone (Sugiyama et al., 1990a,b; Ikeda et al., 1990), which reduce plasma glucose concentrations of non-insulin-dependent diabetes mellitus models due to enhancement of insulin sensitivity in peripheral tissues. As a result of screening for insulin-sensitizing agents, we have discov-

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ered a novel and unique structural compound, JTT-501 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione (Shinkai et al., 1998). In order to investigate whether JTT-501 has different characteristics from the thiazolidinediones, we compared the efficiency and the profile of JTT-501 with pioglitazone and troglitazone using in vitro and in vivo assay techniques.

2. Materials and methods

2.1. Measurement of differentiation of 3T3-L1 cells

The 3T3-L1 fibroblasts (American Type Culture Collection, Rockville, MD) were maintained in Dulbecco's modified Eagles medium (DMEM, Gibco, Grand Island, NY) containing 5% fetal bovine serum (Biocell laboratories, Rancho Dominguez, CA), 100 U/ml penicillin (Gibco), and 100 μg/ml streptomycin (Gibco) in a 75 cm^2 flask (Falcon®, Becton Dickinson, Lincoln Park, NJ) at 37°C in a humidified 95% air, 5% CO_2, atmosphere. Preadipocytes (0.5×10^5 cells/well) were cultured to confluency in 24-well plates (Falcon®) for 2 days, then adipocyte differentiation was initiated by treating confluent preadipocytes with 1 μM dexamethasone (Sigma, St. Louis, MO) and 0.5 mM isobutylmethylxanthine (IBMX, Sigma). After 2 days, the cells were given fresh DMEM containing 2% fetal bovine serum, 10 ng/ml insulin (Sigma) and the test compounds (final concentration 1 nM–10 μM) and allowed to differentiate for an additional 4 days. The cellular lipids were then extracted with 2-propanol and triglyceride concentrations were measured.

2.2. Measurement of peroxisome proliferator-activated (PPA) $_\gamma$ and $_\alpha$ receptors activation

The NIH/3T3 cells (American Type Culture Collection) were maintained in DMEM (Nikken Bio Medical Laboratory, Kanagawa, Japan) containing 10% fetal bovine serum (Moregate, Australia and New Zealand), 50 U/ml penicillin (Gibco), and 50 μg/ml streptomycin (Gibco) at 37°C in a humidified 95% air, 5% CO_2, atmosphere.

The cells (0.4×10^5 cells/well) were cultured in 24-well plates (Falcon®) for 20 h and then transfected with receptor plasmid for the chimera of the PPA_γ receptor or PPA_α receptor ligand binding domain and the GAL4 DNA-binding domain, together with a reporter plasmid containing a GAL4 responsive promoter driving the expression of luciferase. After 5 h, the cells were given fresh DMEM containing 10% fetal bovine serum and the test compounds (final concentration 10 nM–100 μM), and cultured for an additional 2 days. PPA_γ receptor agonist 15-deoxy $\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2, Funakoshi, Tokyo, Japan) and PPA_α receptor agonist 8(*S*)-hydroxy-eicosa-5*Z*,9*E*,11*Z*,14*Z*-tetraenoic acid (8(*S*)-HETE, Funakoshi) were used as positive controls for PPA_γ receptor and PPA_α receptor activation, respectively. After the cells were lysed, luciferase activity was determined with a luminometer CT-9000D (Dia-iatron, Tokyo, Japan).

2.3. Animals

These experiments complied with the Guidelines of Animal Experimentation of our laboratories. Male KK-A^y mice were purchased from Clea Japan, (Tokyo, Japan). Male Zucker diabetic fatty (ZDF) rats (ZDF/Gmi-fa/fa), its lean rats (ZDF/Gmi-lean), and ddY mice were purchased from Charles River Japan (Tokyo, Japan). Male Sprague–Dawley rats were purchased from Japan SLC, (Shizuoka, Japan) and Charles River Japan. The animals were maintained on a standard laboratory chow diet (Oriental Yeast, Tokyo, Japan) and water ad libitum. They were housed in plastic cages in a room controlled for temperature (25 ± 3°C), humidity (55 ± 15%), and light (0800–2000 h).

Eight-week-old ddY mice were rendered diabetic by intraperitoneal injection of streptozotocin (50 mg/kg per day, Sigma) for 5 days. After 2 weeks from the first injection, diabetic mice exhibiting hyperglycemia > 27.8 mmol/l were selected.

2.4. Compounds and administration

JTT-501, troglitazone, and pioglitazone were synthesized at Japan Tobacco, Central Pharmaceutical Research Institute. For cell culture, the compounds were dissolved in dimethyl sulfoxide (Sigma) and added to the medium to a final concentration of 0.1%. For KK-A^y mice, JTT-501 (0.006–0.18%), troglitazone (0.006–0.18%), and pioglitazone (0.0018–0.06%) were given as a dietary admixture in the powdered diet. The doses were estimated from body weight and food consumption. JTT-501 suspended in 0.5% sodium carboxymethylcellulose (CMC–Na, Tokyo Kasei, Tokyo, Japan) solution was administered orally to other animal models once daily by stomach tube.

2.5. Analytical methods

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 radio-immuno assay kit (Shionogi, Tokyo, Japan) with rat insulin (Linco Research, St. Charles, MO) as a standard using an automatic gamma counter, 1470 WIZARD™ (Wallac Oy, Turuk, Finland).

2.6. Measurement of glucose oxidation in adipose tissues

JTT-501 and pioglitazone were administered to KK-A^y mice as food admixture for 4 days. On day 5, epididymal fat pads were removed. Adipose tissue samples were incu-

bated in Hanks' balanced salt solution (Gibco) containing 4% bovine serum albumin (fraction V, Sigma), 20.72 kBq/ml [(*U*)-^{14}C]glucose (NEN, Boston, MA), and 0–100 mU/ml 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 in a scintillation counter, Wallac 1410 (Wallac Oy).

2.7. Statistical analysis

Data are presented as the means ± S.E.M. Statistical analysis was performed with Student's *t*-test and Dunnett's test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. 3T3-L1 cell differentiation

After 4 days' incubation of 3T3-L1 preadipocytes with JTT-501 and 10 ng/ml insulin, cellular triglyceride accumulation was measured as an index of the differentiated adipocyte phenotype. Although JTT-501 did not affect basal differentiation of 3T3-L1 adipocytes, it markedly enhanced insulin-stimulated differentiation (Fig. 1), with an EC_{50} value of 110 ± 43 nM (means ± S.E.M. of three separate experiments). Pioglitazone and troglitazone also enhanced insulin-stimulated differentiation, with EC_{50} values of pioglitazone and troglitazone for an insulin-stimulated differentiation of 155 ± 103 nM (means ± S.E.M. of three separate experiments) and 131 nM (mean of two separate experiments), respectively. In addition, the maximal effects of JTT-501, pioglitazone, and troglitazone were 20 ± 6, 19 ± 4, and 21 μg/well, respectively. Thus, the EC_{50} values and the maximal effects of the three compounds were almost equivalent.

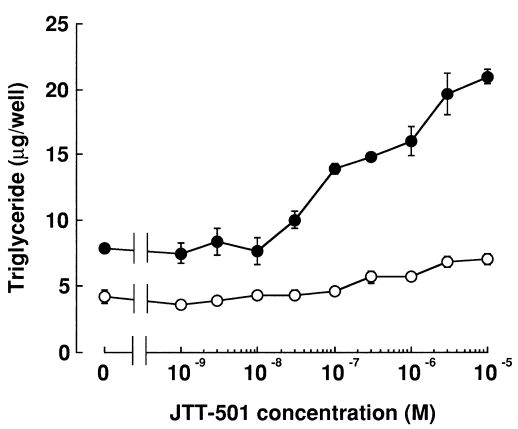

Fig. 1. Effect of JTT-501 on 3T3-L1 cell differentiation. The cells were cultured in medium containing fetal bovine serum (5%), dexamethasone (1 μM), and IBMX (0.5 mM) for 2 days. The cells were then incubated in fresh medium containing fetal bovine serum (2%) and JTT-501 (final concentration 1 nM–10 μM) in the presence (●) or absence (○) of insulin (10 ng/ml) for 4 days. The cellular triglyceride levels were then measured. Each point represents the means ± S.E.M. ($n = 4$).

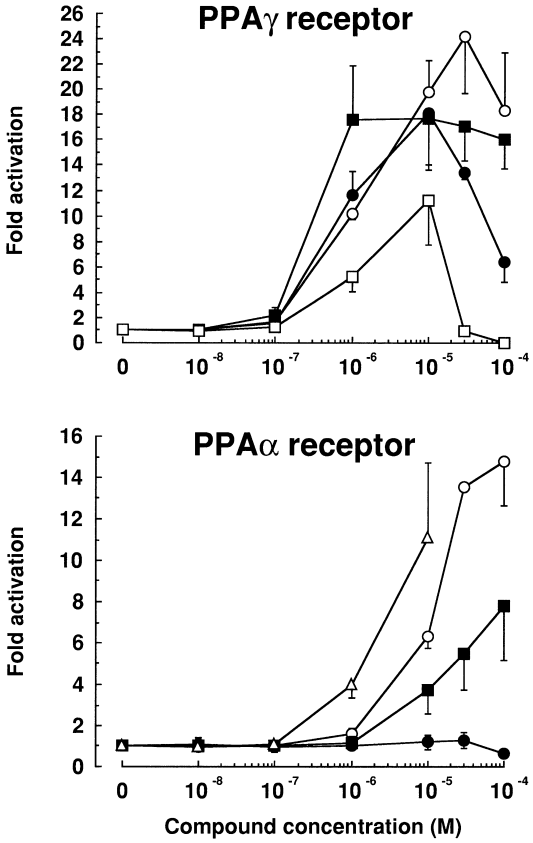

Fig. 2. Effect of JTT-501, pioglitazone, and troglitazone on PPA_γ receptor and PPA_α receptor activation. Cells were transfected with receptor plasmid for the chimera of the PPA_γ receptor or PPA_α receptor ligand binding domain and the GAL4 DNA-binding domain, together with a reporter plasmid containing a GAL4 responsive promoter driving the expression of luciferase. After 5 h, the cells were given fresh medium containing the test compounds (final concentration 10 nM–100 μM), and cultured for an additional 2 days. Luciferase activity was then determined. JTT-501 (○), pioglitazone (■), troglitazone (●), 15d-PGJ_2 (□), 8(*S*)-HETE (Δ). Each point represents the means ± S.E.M. of three separate experiments.

3.2. Effects of JTT-501, pioglitazone, and troglitazone on PPA_γ receptor and PPA_α receptor activation

In the reporter gene assay, JTT-501, pioglitazone, and troglitazone activated PPA_γ receptor as well as the positive control 15d-PGJ_2 (Fig. 2). The $EC_{5\text{-fold}}$ values for PPA_γ receptor activation were 0.28 μM for JTT-501, 0.16 μM for pioglitazone, 0.24 μM for troglitazone, and 1.0 μM for 15d-PGJ_2. On the other hand, JTT-501 and pioglitazone activated PPA_α receptor as well as the positive control 8(*S*)-HETE, but troglitazone did not (Fig. 2). The $EC_{5\text{-fold}}$ values for PPA_α receptor activation were 5.4 μM for JTT-501, 25 μM for pioglitazone, and 1.6 μM for

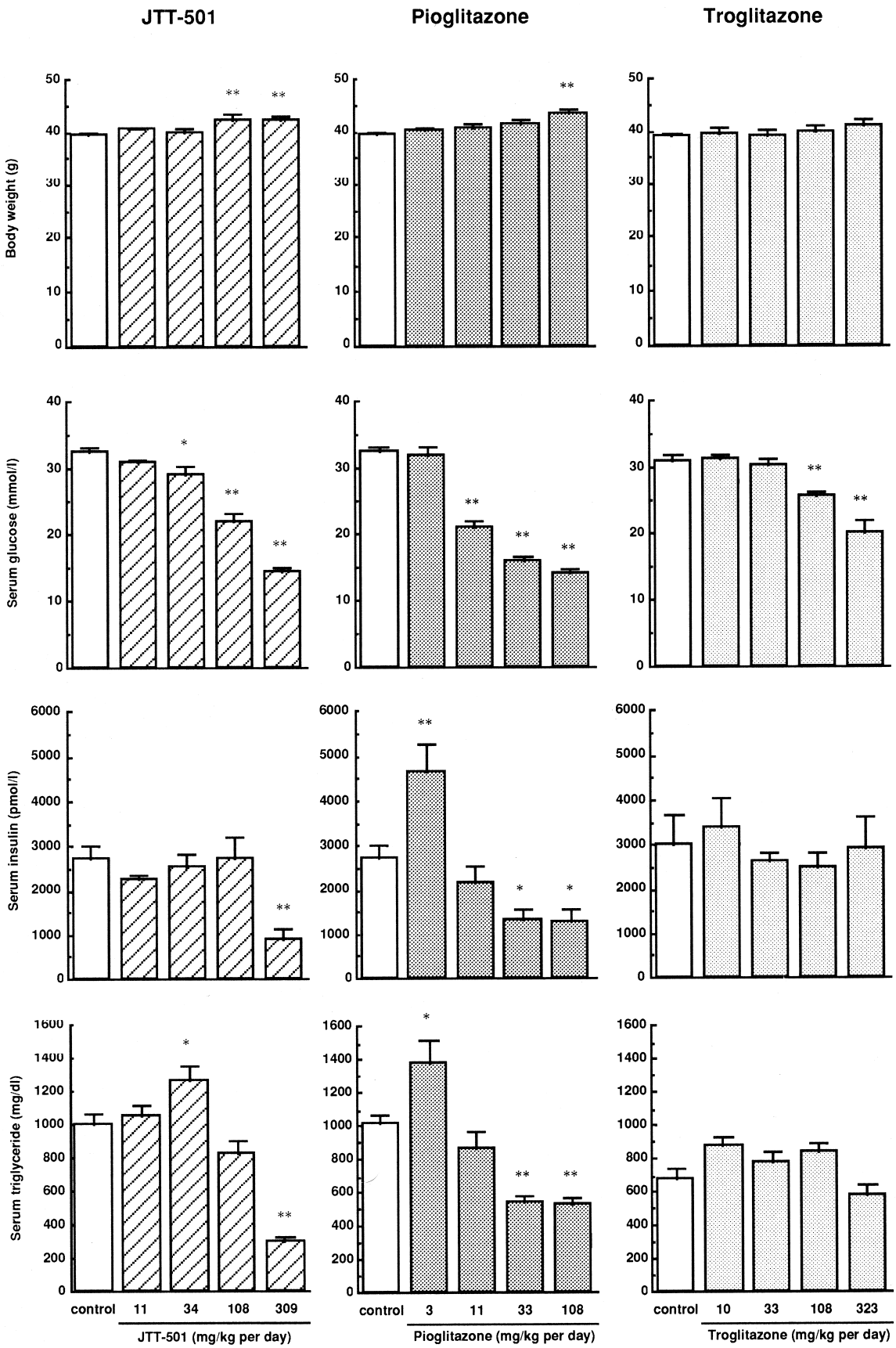
JTT-501
Pioglitazone
Troglitazone
Body weight (g)
Serum glucose (mmol/l)
Serum insulin (pmol/l)
Serum triglyceride (mg/dl)
control 11 34 108 309
JTT-501 (mg/kg per day)
control 3 11 33 108
Pioglitazone (mg/kg per day)
control 10 33 108 323
Troglitazone (mg/kg per day)

Table 1
ED_{50} values of JTT-501, pioglitazone, and troglitazone in KK-A^y mice

Compounds	ED_{50} (mg/kg per day)		
	Glucose	Insulin	Triglyceride
JTT-501	238	234	206
Pioglitazone	30	31	> 108
Troglitazone	> 323	> 323	> 323

The ED_{50} values were determined from the graphs.

8(*S*)-HETE. Furthermore, the efficacy of JTT-501 was greater than that of pioglitazone.

3.3. Effects of JTT-501, pioglitazone, and troglitazone on hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in KK-A^y mice

Non-insulin-dependent diabetes mellitus model KK-A^y mice showed hyperglycemia, hyperinsulinemia, and hypertriglyceridemia (Fig. 3). JTT-501 (11–309 mg/kg per day), pioglitazone (3–108 mg/kg per day), and troglitazone (10–323 mg/kg per day) reduced serum glucose concentrations in a dose-dependent manner. The potency of pioglitazone for glucose and insulin lowering was greater than that of JTT-501 and troglitazone, however, the efficacy of JTT-501 was almost equivalent to that of pioglitazone (Table 1 and Fig. 3). On the other hand, JTT-501 had a greater efficacy than pioglitazone for triglyceride-lowering. In this experiment, troglitazone did not affect serum insulin or triglyceride concentrations.

3.4. Effects of JTT-501 on insulin-stimulated glucose oxidation in KK-A^y mice

Using adipose tissues of KK-A^y mice treated or not with JTT-501 (10–312 mg/kg per day), insulin-stimulated glucose oxidation was measured. Although glucose oxidation levels were slightly stimulated in the control group by insulin, JTT-501 markedly enhanced the insulin-stimulated glucose oxidation levels in a dose-dependent manner (Fig. 4A). Glucose oxidation changes induced by JTT-501 raised the maximal response of adipose tissues to insulin and shifted the insulin-response curve to the left. Pioglitazone (11 mg/kg per day) also enhanced glucose oxidation as well as JTT-501. The equivalent dose of JTT-501 to match the effectiveness of pioglitazone was 48 mg/kg per day (Fig. 4B). Although the potency of pioglitazone was greater than that of JTT-501, this difference was similar to that of the glucose-lowering effects (Table 1).

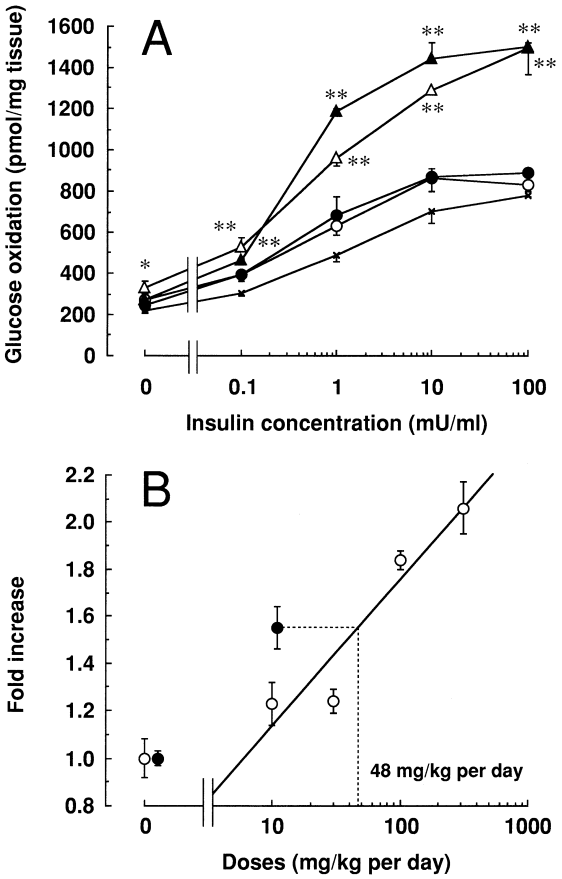

Fig. 4. Effect of JTT-501 and pioglitazone on glucose oxidation in adipose tissues of KK-A^y mice. On day 5, epididymal fat pads were removed. Adipose tissues were incubated in Hanks' balanced salt solution containing glucose (5.6 mM), [(U)-^{14}C]glucose (20.72 kBq/ml), and insulin (0–100 mU/ml) for 2 h at 37°C. Synthesized $^{14}CO_2$ was trapped and counted in a scintillation counter. Panel A shows the effect of JTT-501 on glucose oxidation. Control group (x), JTT-501 10 (○), 30 (●), 102 (Δ), 312 (▲) mg/kg per day group. Each point represents the means ± S.E.M. ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control. Panel B shows the fold increase of JTT-501 (○) and pioglitazone (●) with insulin 10 mU/ml. Each point represents the means ± S.E.M. ($n = 3$).

3.5. Effects of JTT-501 on ZDF rats and streptozotocin-induced diabetic mice

Non-insulin-dependent diabetes mellitus model ZDF rats showed hyperglycemia, hyperinsulinemia, and hypertriglyceridemia compared with lean rats (Fig. 5 left panel). When JTT-501 (30 and 100 mg/kg per day) was administered orally to ZDF rats once daily for 7 days, serum glucose, insulin, and triglyceride concentrations were reduced in a dose-dependent manner. These changes induced by JTT-501 at a 100 mg/kg per day dose were significant.

Fig. 3. Effects of JTT-501, pioglitazone, and troglitazone on serum glucose, insulin, and triglyceride concentrations in KK-A^y mice. JTT-501, pioglitazone, and troglitazone were orally administered to KK-A^y mice (8-week-old) as a food admixture for 4 days. Matched controls were given only standard chow diet for this period. On day 5, blood samples were taken from the orbital sinus. Each column represents the means ± S.E.M. ($n = 7$–8). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control.

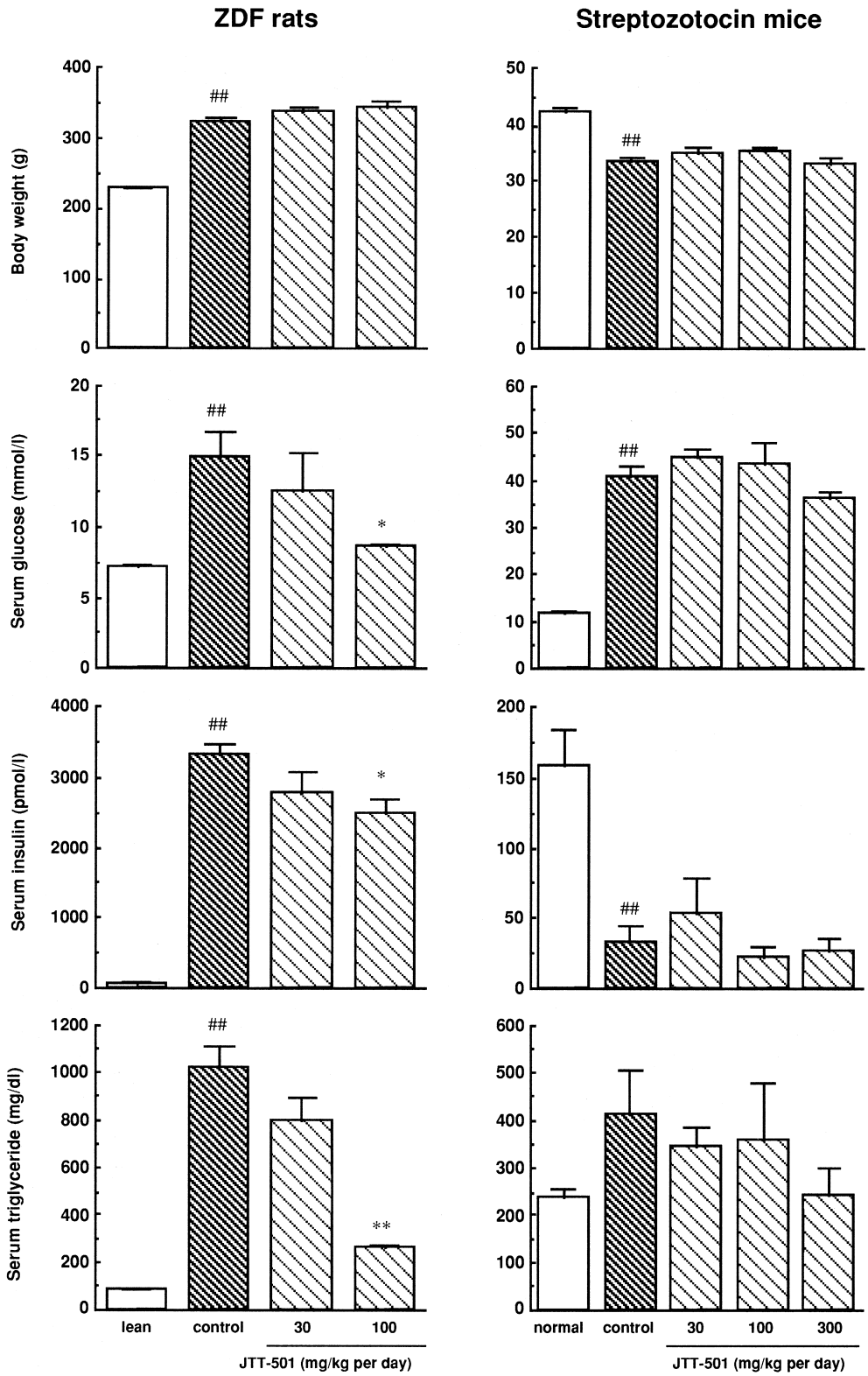

Fig. 5. Effects of JTT-501 on serum glucose, insulin, and triglyceride concentrations in ZDF rats and streptozotocin-induced diabetic mice. JTT-501 was administered orally to male ZDF rats (6 to 7-week-old) for 7 days and to male streptozotocin-induced diabetic mice (10 to 11-week-old) for 7 days. Control group and lean rat or normal mouse groups were treated with 0.5% CMC–Na for this period. Blood samples were taken from the tail vein at 24 h after the last administration. Each column represents the means ± S.E.M. ($n = 7$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control. $^{\#\#}P < 0.01$ vs. lean rats or normal mice.

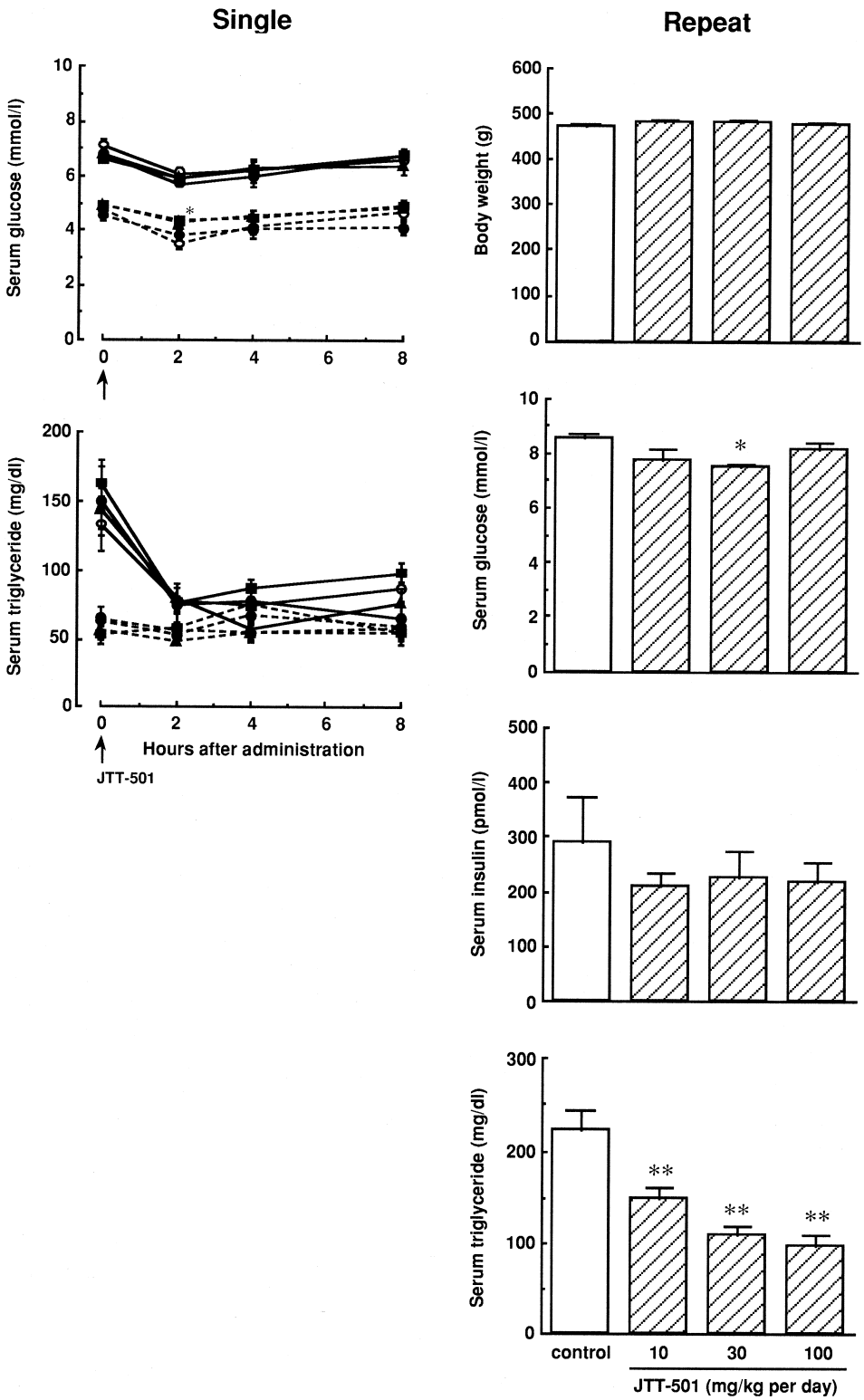

Fig. 6. Effects of single (left panel) and repeat administration (right panel) of JTT-501 on serum glucose or triglyceride concentrations in normal rats. Left panel: single administration of JTT-501. JTT-501 was administered orally to male normal rats (8-week-old) in either the fed state (solid line) or the fasted state (broken line). Control rats were treated with 0.5% CMC–Na. Blood samples were then taken from the tail vein for up to 8 h. Arrow indicates the time of administration. Control group (○), JTT-501 30 (●), 100 (▲), and 300 (■) mg/kg group. Each point represents the means ± S.E.M. ($n = 5$). $* P < 0.05$ vs. control. Right panel: repeat administration of JTT-501. JTT-501 was administered orally to male normal rats (12-week-old) for 4 days. Control rats were treated with 0.5% CMC–Na for this period. Blood samples were taken from the tail vein at 24 h after the last administration. Each column represents the means ± S.E.M. ($n = 6$). $^{*} P < 0.05$, $^{**} P < 0.01$ vs. control.

Insulin-dependent diabetes mellitus model streptozotocin-induced diabetic mice showed hyperglycemia, hypoinsulinemia, and hypertriglyceridemia compared with non-diabetic mice (Fig. 5 right panel). JTT-501 (30, 100, and 300 mg/kg per day) was administered orally to diabetic mice once daily for 7 days. JTT-501 did not affect serum glucose, insulin, or triglyceride concentrations of streptozotocin-induced diabetic mice.

3.6. Effects of JTT-501 on normal rats

In order to investigate whether JTT-501 causes acute hypoglycemia, JTT-501 (30, 100, and 300 mg/kg) was single administered orally to normoglycemic Sprague–Dawley rats both in the fed and the fasted state. JTT-501 did not affect serum glucose or triglyceride concentrations until 8 h after its administration (Fig. 6 left panel). On the other hand, repeated treatment with JTT-501 (10, 30, and 100 mg/kg per day) for 4 days reduced serum triglyceride concentrations in a dose-dependent manner but did not affect serum glucose and insulin concentrations (Fig. 6 right panel).

4. Discussion

JTT-501 is an isoxazolidinedione derivative which is structurally distinct from thiazolidinediones such as troglitazone and pioglitazone. To evaluate its antidiabetic activities, we investigated the effects of JTT-501 on insulin-dependent cell differentiation, activation of PPA receptors, and rodent diabetic models, in comparison with those of troglitazone and pioglitazone. The present study demonstrated that, in non-insulin-dependent diabetes mellitus models, JTT-501 enhances both the sensitivity to, and the potency of, insulin and ameliorates the resistance to insulin.

In the 3T3-L1 cell differentiation assay, troglitazone and pioglitazone, well-known insulin sensitizers, enhanced insulin-dependent 3T3-L1 cell differentiation with EC_{50} values of 155 and 131 nM, respectively, which are in agreement with those in the literature (Kletzien et al., 1991). Under the present experimental conditions, JTT-501 enhanced 3T3-L1 cell differentiation in the presence of insulin with an EC_{50} value of 110 nM, suggesting that JTT-501 is an insulin sensitizer. The insulin-dependent adipocyte differentiation activity of JTT-501 was comparable to that of troglitazone and of pioglitazone. Recently, it has been reported that thiazolidinediones enhance the differentiation of preadipocytes to adipocytes by activating the subtype of PPA_{γ} receptor, and that the activation of this receptor is related to antidiabetic effects (Lehmann et al., 1995; Forman et al., 1995; Kliewer et al., 1995). We also confirmed that JTT-501 similarly activated a PPA_{γ} receptor response element reporter in cells with cotransfected receptor. These results suggest that the antidiabetic effects of JTT-501 may relate to PPA_{γ} receptor activation.

In our experiments, JTT-501 reduced serum glucose and insulin concentrations of KK-A^y mice, with potencies as follows: pioglitazone > JTT-501 > troglitazone, and efficacies of pioglitazone = JTT-501 > troglitazone. The fact that the potencies of JTT-501 and pioglitazone for glucose and insulin lowering were different from the cell differentiation activities of these compounds is considered to be due to differences in bioavailability of the two compounds. Indeed, the bioavailability of JTT-501 is about 30% in rats (unpublished data), while that of pioglitazone is about 90% (Maeshiba et al., 1997). On the other hand, the potencies for triglyceride-lowering were: pioglitazone > JTT-501 > troglitazone, while for glucose and insulin lowering, the efficacies were: JTT-501 > pioglitazone > troglitazone. Furthermore, JTT-501 had a more potent activating effect on PPA_{α} receptor compared with that of pioglitazone and troglitazone. Since these results are well-correlated and it has been reported that PPA_{α} receptor is related to lipid metabolism (Desvergne et al., 1998; Keller et al., 1993), we consider that the PPA_{α} receptor activating effect of JTT-501 plays a role in the potential serum triglyceride lowering. Therefore, it is thought that JTT-501 is not only sufficiently effective for glucose and insulin lowering but also more effective for triglyceride-lowering compared with pioglitazone and troglitazone.

In the glucose oxidation study, JTT-501 elevated the insulin-stimulated glucose oxidation levels in adipose tissues of KK-A^y mice to the same extent as did pioglitazone, suggesting that the antidiabetic effect of JTT-501 is mediated by enhancing insulin sensitivity in peripheral tissues. In addition, JTT-501 was also effective in hyperglycemia in non-insulin-dependent diabetes mellitus model ZDF rats, but not in insulin-dependent diabetes mellitus model streptozotocin-induced diabetic mice. As insulin resistance is a common feature of hyperinsulinemic and hypoinsulinemic conditions (Kahn, 1986), these results suggest that JTT-501 has a specific effect on insulin resistance in the hyperinsulinemic state. This heterogeneity has also been reported with regard to troglitazone and pioglitazone (Fujiwara et al., 1988; Ikeda et al., 1990).

In normal rats, the single or repeated treatment with JTT-501 did not affect basal glucose levels, which is in agreement with results using thiazolidinediones (Fujiwara et al., 1988; Ikeda et al., 1990). Sulfonylureas are the commonly prescribed drugs for hyperglycemia, however, the most frequent severe complication of treatment with sulfonylureas is hypoglycemia (Burge et al., 1998). Our results suggest that JTT-501 does not affect acutely or chronically the basal glucose levels and thus such an event is not expected to occur. In contrast to the effect on blood glucose, repeated treatment with JTT-501 reduced serum triglyceride levels in normal rats. Yamazaki et al. (1997) have recently reported that JTT-501 enhances lipoprotein lipase activity in normal rats and Zucker fatty rats, and

therefore this phenomenon may be mediated through activation of not only PPA_{α} receptor but also lipoprotein lipase by JTT-501.

In conclusion, an isoxazolidinedione derivative, JTT-501, a novel antidiabetic agent, is not only effective for glucose and insulin lowering but also potentially effective for triglyceride-lowering in non-insulin-dependent diabetes mellitus models. However, JTT-501 does not affect the basal glucose level, which is different from sulfonylureas. The activating effect of JTT-501 on not only PPA_{γ} receptor but also PPA_{α} receptor may be responsible for the unique triglyceride-lowering effect compared with pioglitazone and troglitazone. It is expected that JTT-501 will be a novel antidiabetic agent for treating non-insulin-dependent diabetes mellitus patients with insulin resistance.

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