# JTT-501, a New Oral Hypoglycemic Agent, Reverses Hypertriglyceridemia in Zucker Fatty and Ventromedial Hypothalamus-Lesioned Obese Rats

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**JTT-501 is a new oral hypoglycemic agent that is reported to be effective in insulin-resistant diabetic animal models by improving insulin resistance. It also improves hypertriglyceridemia. We investigated the mechanism of the reversal of hypertriglyceridemia in two types of obese animals using JTT-501. In Zucker fatty obese rats, an animal model of genetic obesity, fasting plasma triglyceride and glucose significantly decreased after a single daily oral dose of JTT-501 (100 mg/kg) for 7 days. In ventromedial hypothalamus (VMH)-lesioned obese rats, an animal model of nongenetic obesity, fasting plasma triglycerides significantly decreased but fasting plasma glucose levels remained unchanged after treatment with this agent. In Sprague-Dawley (SD) rats, fasting plasma triglyceride and glucose levels remained unchanged. The JTT-501–treated Zucker fatty and VMH-lesioned obese rats showed a decrease in insulin, but it was not significant, while the treated SD rats showed a significant decrease in insulin. Postheparin plasma lipoprotein lipase (LPL) increased significantly in treated Zucker fatty obese and SD rats, but did not change in VMH-lesioned obese rats. The hepatic triglyceride secretion rate (TGSR) did not change in any species treated with JTT-501. There was a negative correlation between postheparin plasma LPL and plasma triglyceride levels in Zucker fatty obese rats, while no such correlation was observed in VMH-lesioned obese or SD rats. The fractional catabolic rate (FCR) for plasma triglyceride was increased significantly by JTT-501 in both Zucker fatty and VMH-lesioned obese rats. These results suggest that JTT-501 decreases plasma triglycerides mainly by increasing postheparin plasma LPL in Zucker fatty obese rats, while it ameliorates an impairment in the ability of adipose tissue to remove triglyceride from the circulation in VMH-lesioned obese rats.**



INSULIN RESISTANCE is a prominent pathophysiological feature of obese non–insulin-dependent diabetes mellitus (NIDDM),[1-3] and it also plays an important role in regulating triglyceride metabolism.[2,3] Hypertriglyceridemia is frequently found in NIDDM[3-5] and is viewed as a risk factor for cardiovascular disease.[3,5] Therefore, it is important in NIDDM patients to attenuate the hypertriglyceridemia, as well as the hyperglycemia.

Previous reports[6-11] have documented a new class of compounds with a thiazolidine ring, pioglitazone and troglitazone, that appear to ameliorate hyperglycemia by enhancing insulin sensitivity without stimulating insulin secretion in insulin-resistant diabetic animal models. These thiazolidinediones also reportedly have hypolipidemic effects.[7-11]

JTT-501, 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione, is an isoxazolidinedione derivative that is structurally different from thiazolidinedione compounds.[12] This agent was found to improve fasting plasma glucose and insulin levels and glucose tolerance by enhancing insulin sensitivity in diabetic *KK-A$^y$* mice and Zucker fatty obese rats; it also ameliorated hypertriglyceridemia significantly in these animals.[13-16] However, the mechanism by which plasma triglyceride levels decrease after JTT-501 treatment in insulin-resistant diabetic animal models with hypertriglyceridemia remains to be determined. Therefore, this study was undertaken to clarify this mechanism of JTT-501 in Zucker fatty obese rats, an animal model of genetic obesity with insulin resistance,[17,18] and ventromedial hypothalamus (VMH)-lesioned obese rats, another animal model of nongenetic obesity with hypertriglyceridemia.[19,20]

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## MATERIALS AND METHODS

### *Animals*

Female Zucker fatty (*fa/fa*) rats were purchased from Charles River Laboratories (New York, NY). Female Sprague-Dawley (SD) rats were purchased from NRC Haruna (Gunma, Japan). VMH lesions were made in 12-week-old SD rats as previously described.[19] Thirteen-week-old female Zucker fatty obese rats, 20-week-old VMH-lesioned obese rats (8 weeks after VMH lesions), and 14-week-old female SD rats were used for these experiments. The animals were housed in individual wire-bottom cages at constant temperature (24° ± 2°C) and humidity (55% ± 5%) controlled with a 12-hour light-dark cycle. All animals were maintained on laboratory chow (Oriental Yeast, Tokyo, Japan) and had free access to food and water.

### *JTT-501 Administration*

JTT-501 was suspended in 0.5% carboxymethyl cellulose saline and a 100-mg/kg dose was administered to Zucker fatty obese, VMH-lesioned obese, and SD rats intragastrically once per day for 7 days.

Two groups of Zucker fatty obese, VMH-lesioned obese, and SD rats were prepared for experiments to determine postheparin plasma lipoprotein lipase (LPL) and the triglyceride secretion rate (TGSR), respectively: one group for JTT-501 treatment and another group for nontreatment. All experiments were performed after an overnight fast.

### *Plasma LPL*

Under pentobarbital anesthesia (30 mg/kg), 0.7 mL blood was taken from the subclavian venous plexus to measure plasma glucose, triglyceride, and insulin concentrations. Blood was again sampled 3 to 5 minutes after intravenous administration of heparin (200 IU/100 g body weight) to measure plasma LPL. The timing of blood sampling to measure postheparin plasma LPL was based on our previous results.[21] Plasma LPL measurements were performed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (LPL ELISA Daiichi; Daiichi Pure Chemicals, Tokyo, Japan) using an antibovine milk LPL monoclonal antibody.[22]

*TGSR*

Under pentobarbital anesthesia, 0.7-mL blood samples were taken from the subclavian venous plexus to measure plasma glucose, triglyceride, and insulin concentrations. Then, 120 mg Triton WR-1339 (Nakarai Chemical, Tokyo, Japan), a non-ionic detergent, was injected intravenously. Post-Triton samples were collected 30 and 60 minutes thereafter. The samples and sampling times were used to determine TGSR based on the equation,

$$\text{TGSR} = \frac{(\text{TG30} - \text{TG0})/30 + (\text{TG60} - \text{TG0})/60}{2} \times 60,$$

where TG0, TG30, and TG60 represent triglyceride concentrations in plasma collected 0, 30, and 60 minutes after Triton injection.[23,24]

*Fractional Catabolic Rate*

The fractional catabolic rate (FCR) for plasma triglyceride was calculated from the TGSR divided by the plasma pool size as indicated by Bird et al.[25]

*Analytical Methods*

The plasma glucose level was measured by a hexokinase method using a commercially available assay kit (LIQUITECK; Boehringer, Mannheim, Germany). Plasma triglycerides were determined by an enzymatic method using a commercially available assay kit (TRIGLY-COLOR III; Boehringer). Plasma immunoreactive insulin was determined by a double-antibody method using a radioimmunoassay kit (SIONORIA; Shionogi, Osaka, Japan).

*Statistical Analysis*

The data are presented as the mean ± SE and were statistically analyzed by Student's *t* test. The level of significance was a *P* value less than .05.

## RESULTS

There was no difference in final body weight between JTT-501–treated and untreated Zucker fatty obese, VMH-lesioned obese, and SD rats, respectively (Table 1).

*Fasting Plasma Glucose and Insulin*

Fasting plasma glucose levels were significantly lower in JTT-501–treated versus untreated Zucker fatty obese rats, while the levels did not differ in JTT-501–treated and untreated VMH-lesioned obese rats. Following JTT-501 treatment, fasting insulin levels were lower in Zucker fatty obese or VMH-lesioned obese rats than in corresponding untreated Zucker fatty obese or VMH-lesioned obese rats, but these decreases were not significant. Fasting insulin levels were significantly lower in JTT-501–treated SD rats versus untreated SD rats, although plasma glucose levels were not different (Table 2).

*Fasting Plasma Triglyceride*

Fasting plasma triglyceride levels were significantly lower in JTT-501–treated Zucker fatty obese or VMH-lesioned obese rats versus the corresponding untreated Zucker fatty obese or VMH-lesioned obese rats, but there was no difference in triglyceride levels between treated and untreated SD rats (Fig 1).

**Table 2. Effects of JTT-501 on Plasma Glucose and Insulin Levels in Zucker Fatty Obese, VMH-Lesioned Obese, and SD Rats**

| Parameter | SD | Zucker Fatty Obese | VMH-Lesioned Obese |
|---|---|---|---|
| Glucose (mg/dL) | | | |
| Untreated | 90.3 ± 7.9 | 141.9 ± 21.8 | 110.6 ± 6.1 |
| JTT-501 | 83.9 ± 5.2 | 87.5 ± 7.6* | 104.4 ± 7.3 |
| Insulin (ng/mL) | | | |
| Untreated | 0.581 ± 0.123 | 8.256 ± 2.072 | 1.570 ± 0.295 |
| JTT-501 | 0.285 ± 0.028* | 4.276 ± 1.213 | 1.185 ± 0.223 |

NOTE. Values are the mean ± SE of 10 rats in each group.
*$P < .05$ *v* untreated Zucker fatty obese or SD rats, respectively.

*Postheparin Plasma LPL and TGSR*

Postheparin plasma LPL levels were markedly higher in JTT-501–treated Zucker fatty obese or SD rats than in the corresponding untreated Zucker fatty obese or SD rats, but the levels did not change in VMH-lesioned obese rats. There was no difference in the TGSR between JTT-501–treated and untreated Zucker fatty obese, VMH-lesioned obese, or SD rats, respectively (Fig 2).

*Relationship Between Postheparin Plasma LPL and Plasma Triglycerides*

There was a negative correlation between LPL and plasma triglycerides in Zucker fatty obese rats ($r = .744$, $P < .01$). No correlation was observed in VMH-lesioned obese rats or SD rats (Fig 3).

*FCR*

In VMH-lesioned obese and Zucker fatty obese rats, JTT-501 increased the FCR for plasma triglyceride, while the rate did not change in SD rats (Fig 4).

## DISCUSSION

JTT-501 is a new oral hypoglycemic agent that has been shown to have insulin-sensitizing activity and to improve hypertriglyceridemia in diabetic *KK-A$^y$* mice and Zucker fatty rats.[13-16] We examined its effects on hypertriglyceridemia first in Zucker fatty obese rats, an animal model of genetic obesity, and then in VMH-lesioned obese rats, an animal model of nongenetic obesity. JTT-501 induced a significant decrease of fasting plasma triglycerides in both rats with hypertriglyceridemia. We

**Table 1. Body Weight After Treatment With JTT-501 in Zucker Fatty Obese, VMH-Lesioned Obese, and SD Rats**

| | SD | | Zucker Fatty Obese | | VMH-Lesioned Obese | |
|---|---|---|---|---|---|---|
| Body Weight (g) | Untreated | JTT-501 | Untreated | JTT-501 | Untreated | JTT-501 |
| Initial | 272.9 ± 3.5 | 284.9 ± 4.3 | 458.9 ± 11.0 | 454.5 ± 9.6 | 501.5 ± 18.7 | 496.4 ± 12.0 |
| Final | 282.8 ± 3.9 | 297.3 ± 5.6 | 486.4 ± 12.6 | 502.9 ± 10.6 | 499.4 ± 19.5 | 504.7 ± 12.9 |

NOTE. Values are the mean ± SE of 10 rats in each group.

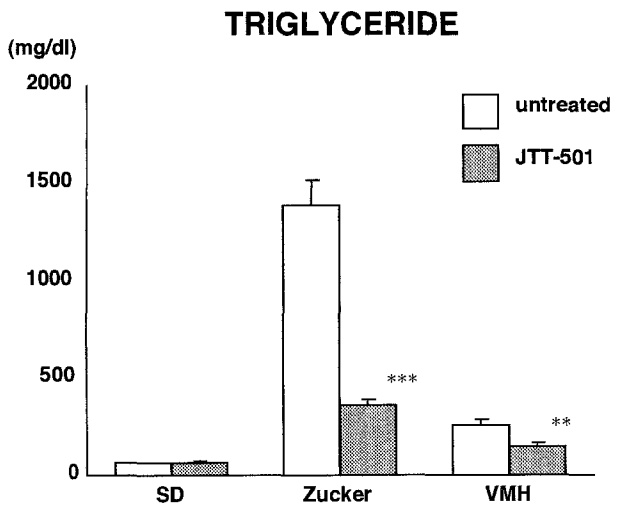


**Fig 1. Effects of JTT-501 on plasma triglyceride levels in Zucker fatty obese, VMH-lesioned obese, and SD rats. Each column represents the mean ± SE (n = 10). **$P < .01$, ***$P < .001$ *v* the corresponding untreated Zucker fatty obese, VMH-lesioned obese, or SD rats, respectively.**

next investigated the mechanism of these hypotriglyceridemic effects.

In general, there are two main factors causing hypertriglyceridemia: (1) a decrease of LPL leading to impaired removal of very–low-density lipoprotein triglyceride (VLDL-TG) and (2) an increase of the hepatic TGSR leading to an elevation of VLDL-TG.[20,23] Thus, we measured both determinant factors: postheparin plasma LPL and the TGSR. Functional LPL resides on the luminal surface of the capillary endothelium,[26-29] and thus we chose to assay heparin-released plasma LPL rather than tissue LPL. The TGSR was determined by measuring the plasma triglyceride level during inhibition of LPL activity by Triton WR-1339.[23]

By measuring both determinant factors, we found that after JTT-501 treatment, postheparin plasma LPL significantly increased but the TGSR was unchanged in Zucker fatty obese rats. Furthermore, there was a negative correlation between postheparin plasma LPL and plasma triglycerides in these rats. These data imply that the decrease in plasma triglycerides after JTT-501 treatment is closely related to the increase in postheparin plasma LPL in Zucker fatty obese rats.

What caused this increase of postheparin plasma LPL in Zucker fatty obese rats after JTT-501 treatment? LPL is subject to regulation by a variety of physiological and pathophysiological situations.[27-29] Postheparin plasma LPL activity can be increased by insulin.[20,27-30] In obese NIDDM and insulin-resistant subjects, postheparin plasma LPL activity is reportedly either normal[31,32] or low[33] despite hyperinsulinemia. Taskinen[27] suggested that these phenomena might be manifestations of insulin resistance. In our study, postheparin plasma LPL increased up to 3 times after treatment with JTT-501, an insulin sensitizer, in Zucker fatty obese rats (to 196.1 ± 23.9 from 61.0 ± 30.2 ng/mL). Thus, it may be reasonable to speculate that LPL did not increase despite high insulin levels because of insulin resistance in Zucker fatty obese rats before JTT-501 treatment, and that postheparin plasma LPL increased with the improved insulin sensitivity in the peripheral tissue of these rats following the treatment.

Recent reports[34,35] have shown that thiazolidinediones are activators (and/or ligands) of the various peroxisome proliferator–activated receptors (PPARs) and that the antidiabetic thiazolidinedione BRL 49653, a high-affinity ligand for PPARγ, induces LPL expression in rat adipose tissue. It is reported that JTT-501 also activates PPARγ and PPARα.[16] Therefore, there is also another possibility that JTT-501 may affect LPL production in adipose tissue via activation of PPARγ, which contributed to the decrease in plasma triglyceride levels in Zucker fatty obese rats.

In VMH-lesioned obese rats, plasma triglycerides were also reduced, although both determinant factors were unchanged after JTT-501 treatment. Why did JTT-501 decrease plasma triglycerides in VMH-lesioned obese rats without changing postheparin plasma LPL and the TGSR? We calculated the FCR for plasma triglyceride from the TGSR divided by the plasma pool size, because it is reported that the VLDL-TG removal capacities estimated by the Triton method and by tracer methods using radiolabeled glycerol are in parallel.[25] JTT-501–treated VMH-lesioned obese rats showed an increased FCR, which means that the half-life of plasma triglyceride was shortened. These results suggest that JTT-501 ameliorates an impairment in the ability to remove triglyceride from the circulation without increasing LPL and/or decreasing the TGSR in VMH-lesioned obese rats. Kazumi et al[36] also reported that pioglitazone, an insulin sensitizer of thiazolidinediones, amelio-

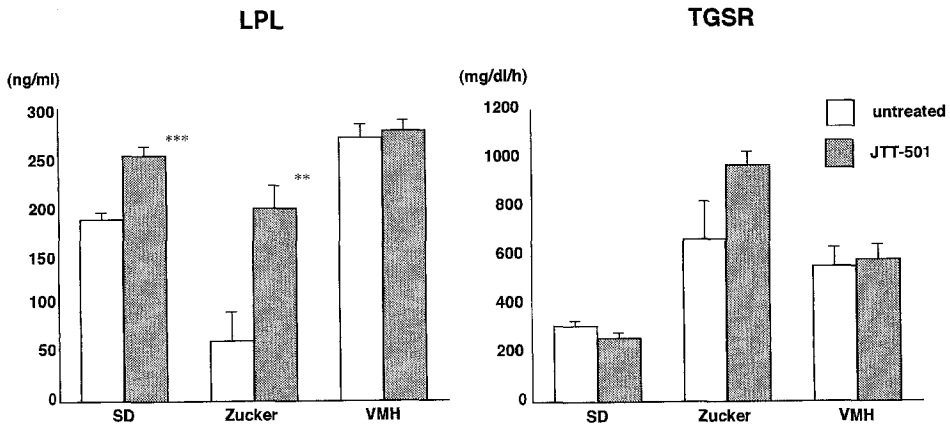


**Fig 2. Effects of JTT-501 on postheparin plasma LPL (n = 5) and TGSR (n = 5) in Zucker fatty obese, VMH-lesioned obese, and SD rats. Each column represents the mean ± SE. **$P < .01$, ***$P < .001$ *v* the corresponding untreated Zucker fatty obese or VMH-lesioned obese rats, respectively.**

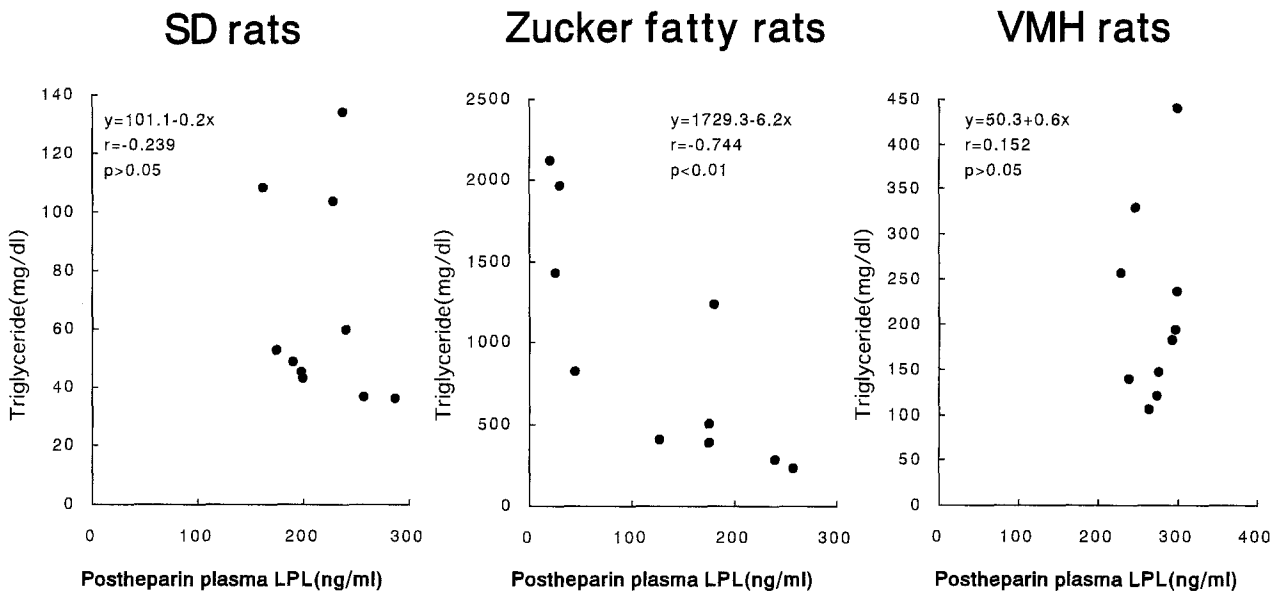


**Fig 3. Relationship between postheparin plasma LPL and plasma triglycerides in Zucker fatty obese, VMH-lesioned obese, and SD rats. Correlations were calculated by linear regression.**

rates hypertriglyceridemia in fructose-fed Wistar fatty rats without changing LPL activity and the TGSR. Okuno et al[37] recently showed that troglitazone increased the number of small adipocytes with normal adipocyte function without changing the white adipose tissue mass, via PPARγ. We previously reported that VMH-lesioned obese rats exhibited hypertriglyceridemia resulting from a limited adipose cell capacity for fat storage, although they showed a high potential ability for plasma triglyceride removal, high LPL activity, and a high capacity for triglyceride production, ie, a high TGSR.[20] If JTT-501 can increase the number of small adipocytes with a strong potential ability for plasma triglyceride removal by activating PPARγ as indicated by Okuno et al,[37] this agent may increase the capacity for fat stores, resulting in a decrease of plasma triglyceride levels in VMH-lesioned obese rats.

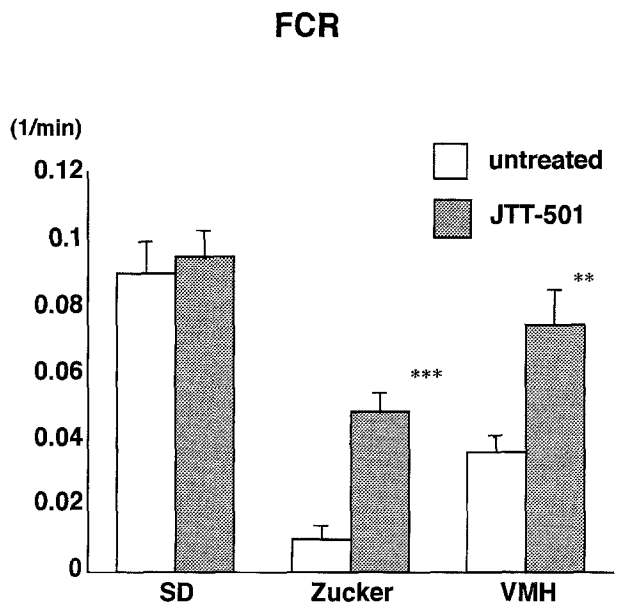


**Fig 4. Effects of JTT-501 on the FCR for plasma triglyceride in Zucker fatty obese, VMH-lesioned obese, and SD rats. Each column represents the mean ± SE (n = 5). **$P < .01$, ***$P < .001$ *v* the corresponding untreated Zucker fatty obese or VMH-lesioned obese rats, respectively.**

It was also shown that JTT-501 increased the FCR in Zucker fatty obese rats. We presume that the increase in postheparin plasma LPL mainly contributed to the enhancement of triglyceride removal. However, a mechanism similar to that in VMH-lesioned obese rats also contributed to some extent.

It has been reported that the antidiabetic thiazolidinediones, pioglitazone[9-10] and troglitazone,[11] decrease plasma triglyceride levels in insulin-resistant diabetic animals. With regard to the mechanism involved in these reductions, Sugiyama et al[10] reported that pioglitazone treatment increased the rate of triglyceride removal but slightly increased hepatic triglyceride output in Wistar fatty rats. Fujiwara et al[11] reported that the rate of lipid removal was enhanced and hepatic triglyceride output was decreased in troglitazone-treated Zucker fatty rats. In our study, JTT-501 similarly enhanced plasma triglyceride removal, but it did not affect the TGSR in either Zucker fatty or VMH-lesioned obese rats. The difference in the results for the TGSR cannot be explained at present; however, it is possible that it may be due to the difference in chemical structures, isoxazolidinedione versus thiazolidinedione.

In conclusion, JTT-501 significantly decreased plasma triglyceride levels in Zucker fatty and VMH-lesioned obese rats by different mechanisms. In Zucker fatty obese rats, JTT-501 mainly contributes to the increase of postheparin plasma LPL, while it may ameliorate the ability of adipose tissue to remove triglyceride from the circulation in VMH-lesioned obese rats, probably via enlargement of the adipose cell capacity for fat storage by increasing the number of small adipocytes. The latter mechanism may also be present in Zucker fatty obese rats, to some extent.

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