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Mechanisms of adipose tissue redistribution with rosiglitazone treatment in various adipose depots

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Abstract

Treatment with thiazolidinediones (TZDs) improves glucose homeostasis by increasing insulin sensitivity, but it also leads to weight gain. Our hypothesis was that, in individual adipose depots, there is depot specificity for lipid storage and energy expenditure genes after TZD treatment. After 5 weeks of rosiglitazone treatment on Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes mellitus with obesity, and Long-Evans Tokushima Otsuka rats as controls, we measured changes in lipid storage and energy expenditure gene expression in various adipose depots, such as mesenteric and nonmesenteric adipose tissues (subcutaneous, epididymal, and retroperitoneal). Mesenteric fat masses did not change after TZD treatment in OLETF rats, but nonmesenteric fat masses increased. Messenger RNA expression of lipid storage genes increased in nonmesenteric fat, but energy expenditure gene expression increased in mesenteric fat after rosiglitazone treatment. In conclusion, our findings suggest that TZD treatment may be associated with the depot-specific effects of lipid storage and energy expenditure genes on fat redistribution in individual adipose tissues in OLETF rats.

1. Introduction

Thiazolidinediones (TZDs), including rosiglitazone (RGZ), are high-affinity ligands for the peroxisome proliferator–activated receptor–γ and are most widely used in the treatment of diabetes mellitus. Long-term treatment with TZDs improves glucose homeostasis by increasing insulin sensitivity in various animal models of obesity [1] and diabetes [2], as well as in humans [3,4]. However, several studies have reported modest weight gains [5] in diabetes subjects treated with TZDs due to edema [6,7] or fat accumulation [8-13].

Thiazolidinediones increase subcutaneous adipose tissue but decrease or do not affect visceral adipose tissue related to insulin resistance [8-13]. The mechanisms of the effect of TZD on adipose tissue have not been clearly identified. One possible hypothesis is that TZD promotes differentiation of preadipocytes in subcutaneous fat but does not have the same effect on preadipocyte in visceral fat and, therefore, the effect of TZD will vary according to the type of fat [14-16]. An alternative hypothesis is that TZDs result in the depot-specific regulation of lipid uptake and energy expenditure genes in visceral and subcutaneous fat [17,18]. Although adipose remodeling with TZD treatment is a well-established phenomenon, the mechanisms by which it occurs and the changes in the individual adipose depots are not fully understood. The aim of this study is to examine the effects of RGZ on genes related to lipid storage and energy expenditure in mesenteric and nonmesenteric (subcutaneous, epididymal, and retroperitoneal depots) adipose tissues of

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Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes mellitus.

2. Materials and methods

2.1. Animal and experimental protocol

All procedures were performed in accordance with institutional guidelines for animal research. For the type 2 diabetes mellitus with obesity animal models, 10 male OLETF rats and the control group of 8 male Long-Evans Tokushima Otsuka (LETO) rats were sent from Tokushima Research Institute, Otsuka Pharmaceutical (Tokushima, Japan), as 4-week–old mice. They were maintained in the Animal Care Center at the Kangbuk Samsung Hospital, Seoul, South Korea, under controlled temperatures (23°C ± 2°C) and humidity (55% ± 5%) under a 12-hour day and 12-hour night setting. The rats were fed standard rat chow until the age of 29 weeks. At the age of 29 weeks, the rats were randomly divided into standard diet (control group) and standard diet and RGZ (3 mg/kg/d) (treatment group) for 5 weeks.

2.2. Intraperitoneal glucose tolerance test

At the age of 29 weeks, the OLETF and LETO rats were placed under fasting conditions for 16 hours and were intraperitoneally given glucose (2 g/kg) before and after the 5-week treatment. Blood samples were collected from the tails at 0, 15, 30, 60, 90, and 120 minutes after the glucose load. The glucose levels were measured with a glucose analyzer (GlucoDr; Allmedicus, Anyang, Korea).

2.3. Plasma glucose, insulin, and lipid measurements

Plasma glucose levels were measured by the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay using the double-antibody method with a commercially available radioimmunoassay kit (Linco Research, St Charles, MO). Plasma concentrations of triglycerides and free fatty acid (FFA) levels were measured by enzymatic colorimetric methods using commercially available kits.

2.4. Fat tissue sample

After the 5-week period, the rats were decapitated. Mesenteric, subcutaneous, epididymal, and retroperitoneal adipose tissues were dissected after midabdominal incision; and the weight of each sample of dissected fat tissue was determined immediately.

2.5. Real-time reverse transcriptase polymerase chain reaction

The total RNA was extracted using TRI Reagent (MRC, Cincinnati, OH) according to the manufacturer's instructions. One microgram of RNA was reverse transcribed using the Molony murine leukemia virus reverse transcriptase (SUPER-Bio, Suwon, Korea) with random hexamer primers. The resultant complementary DNA was amplified using real-time polymerase chain reaction (PCR) (Exicycler; Bioneer, Daejeon, Korea). Glycerol-related genes, such as glycerol kinase (*Gyk*), phosphoenolpyruvate carboxykinase (*PEPCK*), and aquaporin adipose (*AQPap7*); fatty acid–related genes such as lipoprotein lipase (*LPL*), hormone-sensitive lipase (*HSL*), fatty acid transport protein (*FATP*), acetyl-CoA carboxylase–α (*ACC*), and fatty acid synthase (*FAS*); and energy expenditure–related genes, such as uncoupling proteins (*UCP1*, *2*, and *3*) and carnitine palmityl transferase–1 (*CPT-1*), messenger RNA (mRNA) levels were measured by real-time reverse transcriptase (RT) PCR using β-actin as a control. The sequences and sizes of each gene are listed in Table 1.

The PCRs were performed in a 20-μL–volume 96-well plate with 1 μL RT product, 0.5 μmol/L primer, and 4 mmol/L $MgCl_2$. The *Taq* polymerase, PCR buffer, dNTPs, and SYBR Green I mix were purchased from Bioneer. The thermal cycling profile consisted of a preincubation step at 95 °C for 10 minutes, followed by 40 or 50 cycles of a 95°C denaturation step for 10 seconds, a 60°C annealing step for 5 seconds, and a 72°C extension step for 20 seconds. The

Table 1
Sense/antisense sets and sizes of oligonucleotide sequences

Gene (rat)	Sense	Antisense	Size (base pairs)
Gyk	CAATTGGTTGGGTTACAACT	GTCTGCTTAGAGGATCATGC	191
PEPCK	GACAAGTATCTGGAGGACCA	TCTACTCAGCATTGTGCTTG	186
GLUT4	TACTTAGGGCCAGATGAGAA	AATCACACAGAGGGAATGAG	194
AQPap7	TTCCCTATATATGTGCTGGG	ACCTGTCACCAACAGTTCTC	117
LPL	CTTCTTGATTTACACGGAGG	GATCTTCTCGATGACAAAGC	124
HSL	CTCCGTGCTCTAGCCTACTA	CTGTGAGTCTGGAAGGACAT	192
FATP	TGCTCTATGACTGCCTACCT	ATATTTGACACAGTCGTCCC	118
ACC	CTGTGAGGTGGATCAGAGAT	TTCAGCTCTAACTGGAAAGC	129
FAS	TTTCCAAGATTCAAATTGCT	CATTTTTACCAGGTTGGTGT	104
CPT-1	GTGTTGGAGGTGACAGACTT	CACTTTCTCTTTCCACAAGG	101
UCP2	GGAGATACCAGAGCACTGTC	ATGAGGTCATAGGTCACCAG	139
UCP3	TCTCACCTGTTCACTGACAA	TCTCACCTGTTCACTGACAA	107

annealing and detection temperatures for the primers were 50°C. At the end of the PCR, a melting curve analysis was performed by gradually increasing the temperature from 70°C to 90°C (0.1°C/s) to confirm the amplification specificity of the PCR products.

The level of expression of each mRNA and their estimated crossing points for each sample were determined relative to the standard preparation using Bioneer computer software. The PCR standard for *β*-actin, *Gyk*, *PEPCK*, *GLUT4*, *AQPap7*, *LPL*, *HSL*, *FATP*, *ACC*, *FAS*, *UCP2* and *3*, and *CPT-1* consisted of a known number of molecules of the PCR product; this was purified using a gel extraction kit (Altman BioScience, Uiwang, Korea) and then quantified spectrophotometrically. The mRNA expression of all genes reported was normalized to the *β*-actin expression level. The standards were made to a concentration of 10^8 copies per microliter. The PCR amplification was performed with a series of standard curves that were automatically generated. A standard curve was constructed for each PCR run. All the samples to be compared were run in the same assay.

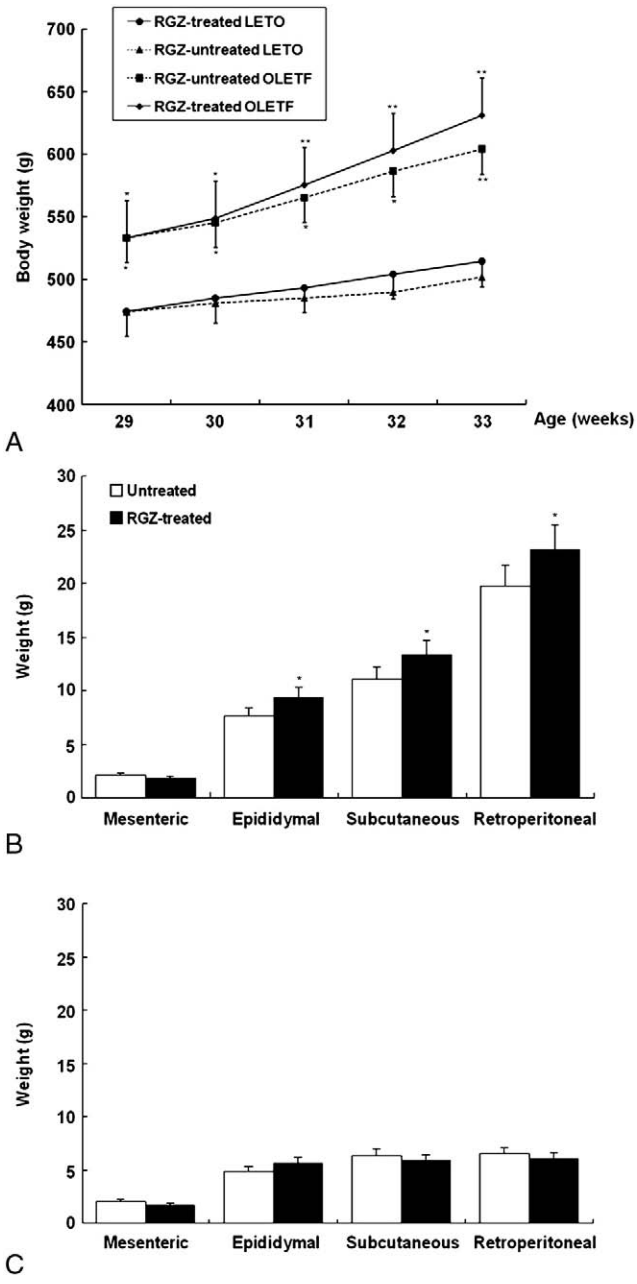

Fig. 1. Effect of RGZ after 5 weeks of treatment on body weights (A) and on mesenteric and nonmesenteric (subcutaneous, epididymal, and retroperitoneal) fat masses in OLETF (B) and LETO (C) rats. *$P < .05$, **$P < .01$ vs RGZ-untreated LETO rats. *$P < .05$ vs untreated group. Results are means ± SD.

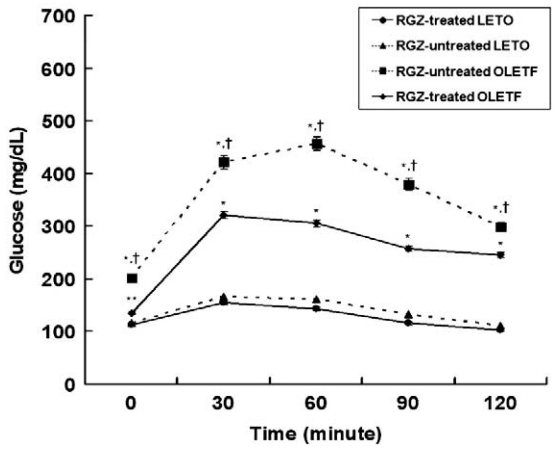

Fig. 2. Changes of plasma glucose concentration during intraperitoneal glucose tolerance test after 5 weeks of treatment. *$P < .001$, **$P < .05$ vs RGZ-untreated LETO rats. $^{\dagger}P < .001$ vs RGZ-treated OLETF rats. Results are means ± SD.

2.6. Statistical analyses

The data used for statistics are reported as mean ± standard deviation. Statistical analyses were performed with statistical analysis software for PC (SPSS 12.0; Microsoft,

Table 2
Biochemical data after 5 weeks of treatment

	RGZ-untreated LETO	RGZ-treated LETO	RGZ-untreated OLETF	RGZ-treated OLETF
Fasting glucose (mg/dL)	116.3 ± 11.8	113.3 ± 14.8	201.6 ± 33.9*	135.4 ± 18.5‡
Fasting insulin (μIU/mL)	10.5 ± 2.9	6.8 ± 4.5	21.1 ± 5.2†	7.0 ± 2.4§
Triglyceride (mg/dL)	92.8 ± 17.4	89.5 ± 46.6	356 ± 111.5†	107.4 ± 30.8§
FFA (μEq/L)	279.3 ± 40.3	242.5 ± 50.7	627.2 ± 172.6†	338 ± 97.1‡

Data are mean ± SD.
* $P < .05$ vs RGZ-untreated LETO rats.
† $P < .01$ vs RGZ-untreated LETO rats.
‡ $P < .05$ vs RGZ-untreated OLETF rats.
§ $P < .01$ vs RGZ-untreated OLETF rats.

Seattle, WA) along with application of the Student *t* test as well as analysis of variance. The *statistical significance* was defined as $P < .05$.

3. Results

3.1. Change in weight and fat distribution

At the age of 29 weeks, the OLETF rats had a significantly higher body weight compared with the LETO rats. After 5 weeks of treatment, the OLETF rats fed a standard diet with RGZ had significantly higher body weight than the OLETF rats fed only a standard diet (631.2 ± 24.4 g in the treatment group vs 533 ± 15.8 g in the control group, $P < .01$) (Fig. 1A). Rosiglitazone treatment had no influence on the amount of food intake within the same species group (43.46 ± 7.1 g/d in RGZ-untreated OLETF vs 45.16 ± 4.1 g/d in treated OLETF, P = not significant; 26.85 ± 4.7 g/d in RGZ-untreated LETO vs 27.6 ± 2.1 g/d in treated LETO, P = not significant).

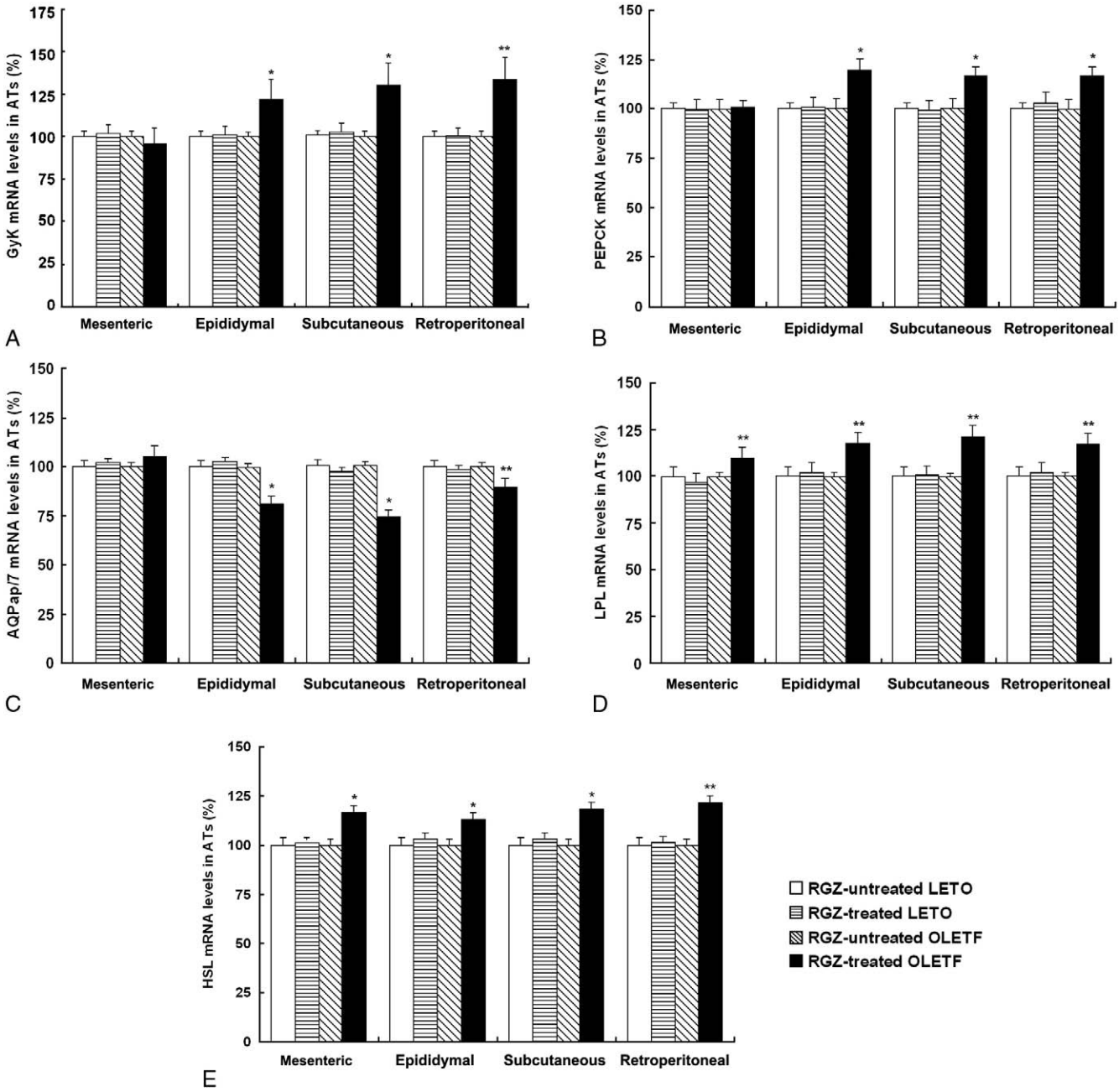

Fig. 3. Effects of RGZ on the expression of *Gyk*, *PEPCK*, *AQPap7*, *LPL*, and *HSL* mRNA in the mesenteric, epididymal, subcutaneous, and retroperitoneal fat depots of LETO and OLETF rats. The *Gyk* (A), *PEPCK* (B), *AQPap7* (C), *LPL* (D), and *HSL* (E) mRNA expressions were measured by real-time RT-PCR. *$P < .05$, **$P < .01$ compared with the RGZ-untreated LETO rat group. Data were normalized using β-actin mRNA and expressed as a percentage of the value obtained from control, untreated LETO rats. Results are means ± SD.

Rosiglitazone-treated OLETF rats showed a significant increase in subcutaneous (11.06 ± 1.40 g vs 13.37 ± 0.97 g, $P < .05$), epididymal (7.66 ± 1.09 g vs 9.93 ± 1.62 g, $P < .05$), and retroperitoneal (21.03 ± 3.49 g vs 24.35 ± 3.32 g, $P < .05$) depots; but there was no difference in the mesenteric fat weight between the RGZ-treated OLETF rats and the control group. The LETO rats did not show any significant change in fat distribution (Fig. 1B, C).

3.2. Intraperitoneal glucose tolerance test

Both the OLETF and LETO rats showed the highest blood glucose levels at 30 to 60 minutes after the glucose injection following fasting, and blood glucose levels gradually decreased thereafter (Fig. 2). Plasma glucose concentrations were significantly increased in both RGZ-untreated and RGZ-treated OLETF rats compared with untreated LETO rats at all time points measured after intraperitoneal glucose load. There was no statistically significant difference in the glucose level between RGZ-untreated and RGZ-treated LETO rats. However, RGZ treatment induced a significantly decreased plasma glucose concentration in OLETF rats.

3.3. Plasma glucose, serum insulin, and lipid concentrations

As shown in Table 2, plasma glucose and FFA levels measured after 5 weeks of treatment had significantly decreased in RGZ-treated OLETF rats compared with untreated OLETF rats ($P < .05$, each). The concentration of serum triglyceride had significantly ($P < .01$) decreased in RGZ-treated OLETF rats. The OLETF rats were also significantly hyperinsulinemic compared with RGZ-untreated LETO rats ($P < .01$), and the hyperinsulinemia of OLETF rats was markedly ameliorated after 5 weeks of RGZ treatment ($P < .05$).

3.4. Energy storage–related genes analyses

3.4.1. Glycerol-related genes analyses

The *Gyk* gene, which converts glycerol to glycerol 3-p, showed a significant increase in expression in subcutaneous fat (130.44% ± 28.36%, $P < .05$), epididymal fat (121.58% ± 16.6%, $P < .05$), and retroperitoneal fat (130.29% ± 7.68%, $P < .01$) in the RGZ-treated OLETF rats but did not show a significant change in mesenteric fat (Fig. 3A). The *PEPCK*

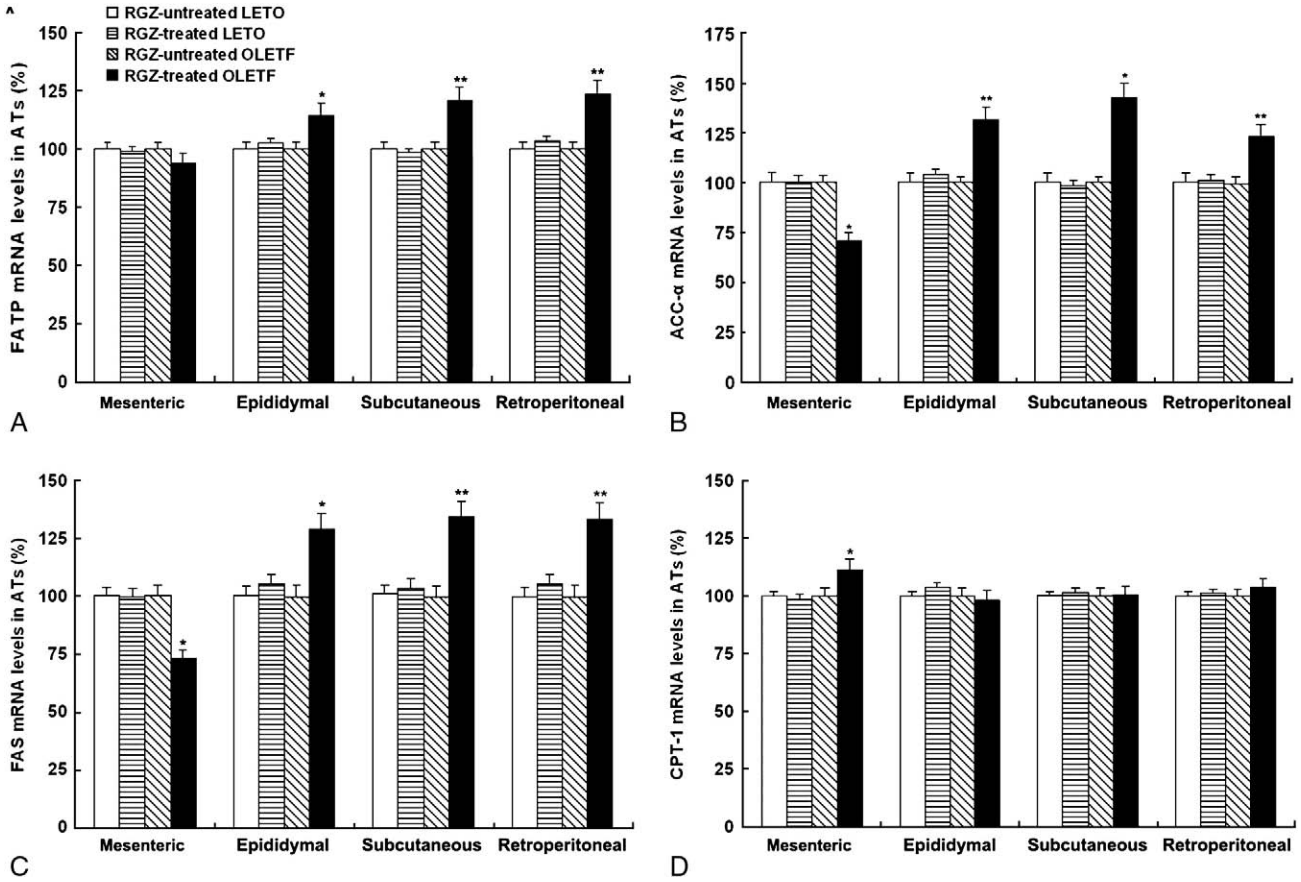

Fig. 4. Effects of treatment with RGZ on the expression of *FATP*, *ACC-α*, *FAS*, and *CPT-1* mRNA in the mesenteric, epididymal, subcutaneous, and retroperitoneal fat depots of LETO and OLETF rats. The *FATP* (A), *ACC-α* (B), *FAS* (C), and *CPT-1* (D) mRNA expressions were measured in real-time RT-PCR. *$P < .05$, **$P < .01$ compared with the RGZ-untreated LETO rat group. Data were normalized using *β*-actin mRNA and expressed as a percentage of the value obtained from control, untreated LETO rats. Results are means ± SD.

gene, which is related to de novo synthesis, showed a significant increase in subcutaneous fat (116.60% ± 6.08%, $P < .05$), epididymal fat (119.36% ± 14.97%, $P < .05$), and retroperitoneal fat (116.65% ± 9.80%, $P < .05$) in the RGZ-treated OLETF rats, but did not show a significant change in mesenteric fat (Fig. 3B). The *AQ-Pap7* gene, which is related to efflux of glycerol, showed a significant decrease in activation in subcutaneous fat (74.18% ± 9.45%, $P < .05$), epididymal fat (80.83% ± 4.09%, $P < .05$), and retroperitoneal fat (89.27% ± 2.81%, $P < .01$), although it did not show any significant change in mesenteric fat (Fig. 3C).

3.4.2. Fatty acid–related genes analyses

3.4.2.1. Lipolysis and transport of fatty acid–related genes. Lipoprotein lipase and *HSL*, which are both related to lipolysis, showed an increase in all parts of the fat tissue collected from the RGZ-treated OLETF rats (Fig. 3D, E). Fatty acid transport protein, which is related to fatty acid influx into adipose cells, showed increased activation in subcutaneous fat (120.73% ± 12.04%, $P < .05$), epididymal fat (114.08% ± 11.25%, $P < .05$), and retroperitoneal fat (123.59% ± 6.72%, $P < .05$) in the RGZ-treated OLETF rats but no significant change in mesenteric fat (Fig. 4A).

3.4.2.2. De novo synthesis–related genes. Acetyl-CoA carboxylase–α , which is involved in de novo synthesis of fatty acids, showed a significant increase in subcutaneous fat (142.38% ± 23.64%, $P < .05$), epididymal fat (131.43% ± 14.27%, $P < .05$), and retroperitoneal fat (122.83% ± 8.23%, $P < .05$) in the RGZ-treated OLETF rats and showed a significant decrease in mesenteric fat (71.13% ± 11.72%, $P < .05$) (Fig. 4B). Fatty acid synthase also showed a significant increase in subcutaneous fat (133.95% ± 10.34%, $P < .05$), epididymal fat (129.20% ± 19.32%, $P < .05$), and retroperitoneal fat (133.42% ± 6.70%, $P < .05$) in the RGZ-treated OLETF rats; however, it showed decreased activation in mesenteric fat (73.04% ± 17.88%, $P < .05$) (Fig. 4C).

3.5. Energy expenditure–related genes analyses

Carnitine palmityl transferase–1, which is related to β-oxidation of fatty acid in mitochondria, showed a significant increase in mesenteric fat (111.36% ± 7.10%, $P < .05$) in the RGZ-treated OLETF rats (Fig. 4D). Uncoupling protein isoform expression, which is related to thermogenesis in white adipose tissue, was also examined. Uncoupling protein–2 gene expression was increased significantly in mesenteric and nonmesenteric adipose tissues, but the *UCP3* gene showed no significant change in both depots (data not shown).

4. Discussion

The present study demonstrates the depot-specific regulation of lipid storage and energy expenditure genes in individual adipose tissues in OLETF rats after RGZ treatment. We found that RGZ treatment increased in the nonmesenteric depots but not in the mesenteric depot and improved insulin sensitivity, accompanied by suppression of plasma FFA. We also found that mRNA expression of lipid storage genes was increased in the nonmesenteric depots in the RGZ-treated OLETF rats and that expression of energy expenditure genes was increased in the mesenteric depot. The LETO rats did not show any significant change in either type of fat depots. These results suggest that TZD treatment may be associated with some depot-specific effects of lipid storage and energy expenditure genes in individual adipose tissues on fat redistribution.

Thiazolidinedione, which has an insulin-sensitizing action via the stimulation of peroxisome proliferator–activated receptor–γ, exerts pluripotent effects on many cell types [19,20] and is used clinically to treat type 2 diabetes mellitus. However, long-term TZD therapy increases overall adiposity and promotes weight gain in both rats and humans [21]. Possible mechanisms leading to these effects of TZD therapy are increase in body fluids [22], increased appetite [23], decrease in glucosuria [24], decreased synthesis of leptin [22], and differentiation of adipose cells [19]. In regard to differentiation of adipose cells, a previous study has shown that TZD treatment markedly enhanced the differentiation of preadipocytes from subcutaneous sites. In contrast, preadipocytes from omental sites were refractory to TZDs [16]. However, another report found no difference in preadipocytes between subcutaneous and omental regions and that they were augmented to the same extent by treating with various TZDs (RGZ, pioglitazone, or troglitazone) in the 2 depots [25].

Another possible mechanism, including our hypothesis, is that TZD treatment may lead to the depot-specific regulation of lipid storage and energy expenditure genes in both mesenteric and nonmesenteric depots. Although adipose remodeling with TZD treatment is a well-established phenomenon in animal models [1,17,26] and in humans [10,12,27], the mechanisms by which it occurs in the various adipose depots are not fully established. To our knowledge, a few studies have reported that TZDs redistribute adipose tissues by depot-specific regulation of lipid uptake and energy expenditure genes in visceral and subcutaneous fat [17,18]. These studies [17,18] suggested that TZD treatment increased the subcutaneous fat mass and reduced visceral fat accretion by stimulating lipid uptake and esterification potential in subcutaneous fat. Conversely, lipid uptake is minimally altered and energy expenditure is greatly increased in visceral fat, with a consequent reduction in fat accumulation. However, there are some differences between these previous studies [17,18] and our report. First, the species used were different; male Sprague-Dawley rats were

used in these studies [17,18]. Another study [1] showed the effects of TZD in adipose tissue remodeling in Zucker fatty rats as an obesity and insulin resistance model. These animal models were not representative of type 2 diabetes mellitus, for which condition TZDs are commonly used in clinical practice. Our study used OLETF rats as the type 2 diabetes mellitus with obesity model and LETO rats as the normal but obese control model. The LETO rats did not show any significant change in either type of fat depots. This may be due to differences in the model species. Second, in previous studies [17,18], retroperitoneal adipose tissue was classed as representative of visceral fat. The present study examines the effects of RGZ on mRNA expressions of lipid storage and energy expenditure genes in mesenteric, subcutaneous, epididymal, and retroperitoneal adipose tissues. Our results are different from previous reports [17,18] in terms of retroperitoneal and mesenteric depots. Our study found that RGZ-treated OLETF rats showed a significant increase in the retroperitoneal depot, but we found no difference in the mesenteric depot of RGZ-treated OLETF rats. We also found that mRNA expressions with RGZ treatment in the mesenteric depot were different from those in the retroperitoneal fat. Although there are less marked regional variations between subcutaneous and visceral depots in metabolic and endocrine activities in rodent models than in human subjects [27,28], some animal model studies have used omental [28] and mesenteric [2] adipose tissues as representative of visceral fat.

Our results showed only a modest RGZ effect on adipose weight and gene expression compared with previous reports [2,17,29-31]. We are not able to explain the above discrepancies. However, the expressions of fatty acid–related genes such as *ACC*-α and *FAS*, 2 genes for fatty acid storage as triglycerides in adipose tissue, were up-regulated by RGZ treatment in nonmesenteric depots and down-regulated in mesenteric depot. These different responses of the gene expressions to the RGZ treatment in both depots suggest that the regulation of fatty acid–related genes with RGZ treatment may play an important role in terms of fat redistribution.

The results of our study are summarized in Online Supplementary Figure 1, which shows the proposed model for the effects of TZD treatment on the depot-specific regulation of lipid storage and energy expenditure genes in nonmesenteric and mesenteric fat.

The limitation of the present animal study was that the effects of TZD treatment on the changes of gene expression to functional lipid uptake and oxidation, and the relationship of protein level and/or enzyme activity to gene expressions were not evaluated in both rat models. Thus, further work is needed to elucidate these questions. However, to our knowledge, this study is the first report showing that RGZ has depot-specific effects on fat redistribution in various adipose depots in OLETF rats (as an animal model of type 2 diabetes mellitus with obesity) and LETO rats (as a normal but obese control model). In conclusion, our findings suggest that TZD treatment may be associated with the depot-specific effects of lipid storage and energy expenditure genes on fat redistribution in individual adipose tissues in OLETF rats.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2009.07.004.

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