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Effect of PPAR-δ agonist on the expression of visfatin, adiponectin, and resistin in rat adipose tissue and 3T3-L1 adipocytes

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Abstract

It has been recently reported that activation of PPAR-δ, by specific agonists or genetic manipulation, alleviates dyslipidemia, hyperglycemia, and insulin resistance in animal models of obesity and type 2 diabetes. The purpose of the present study was to determine whether the PPAR-δ agonist has a direct effect on adipokines in visceral adipose tissue of rats and in cultured adipocytes. We examined the expression of visfatin, adiponectin, and resistin mRNA in visceral adipose tissue of Wistar rats fed a high-fat diet and 3T3-L1 adipocytes treated with PPAR-δ agonist (L-165041). Body weight and biochemical measurements were performed.

Rats fed a high-fat diet showed a greater increase in body weight than those fed a standard diet ($P < 0.05$), and treatment with L-165041 (10 mg/kg/day) significantly decreased weight gain ($P < 0.05$). The concentration of total cholesterol was lower, and HDL cholesterol was higher in L-165041-treated rats ($P < 0.05$). In the visceral adipose tissue of L-165041-treated rats, visfatin and adiponectin mRNA levels significantly increased compared to those of the untreated rats ($P < 0.05$). However, the expression of resistin decreased in the L-165041-treated rats. Furthermore, in cultured 3T3-L1 adipocytes, the level of visfatin and adiponectin mRNA was up-regulated in response to L-165041 treatment for nine days. By contrast, resistin mRNA levels were down-regulated by L-165041 treatment. The present study provides a novel evidence to suggest that the PPAR-δ agonist has regulatory effects on a variety of adipokines, and these effects might explain some of their metabolic function.

Keywords: Peroxisome proliferator-activated receptor delta; Adipokine; Visfatin; Adiponectin; Resistin; Metabolic syndrome

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear receptor superfamily. These lipid sensors are key transcriptional regulators of nutrient metabolism and energy homeostasis. Agonists of PPAR-α (fibrates) and PPAR-γ (thiazolidinediones) are used clinically for the treatment of dyslipidemia and type 2 diabetes, respectively. Recent studies have reported that activation of PPAR-δ, by specific agonists or genetic manipulation, alleviates dyslipidemia, hyperglycemia, and insulin resistance in animal models of obesity and type 2 diabetes [1–3]. The beneficial effects of PPAR-δ have been ascribed to enhancement of fatty acid catabolism and energy uncoupling, resulting in elevated energy expenditure and fat dissipation [3,4]. Therefore, PPAR-δ is considered to be a promising therapeutic target for the metabolic syndromes [5].

Although the pathophysiologic mechanisms underlying the metabolic syndrome are incompletely understood, insulin resistance appears to be an important component [6]. Adipokines, such as adiponectin, leptin, TNF-α, resistin,

Abbreviations: PPARs, peroxisome proliferator activated receptors; TZDs, thiazolidinediones; FFAs, free fatty acids; FBS, fetal bovine serum; qRTRT-PCR, quantitative real time reverse transcription polymerase chain reaction.

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and visfatin, are thought to provide an important link between obesity, insulin resistance and inflammatory disorders including cardiovascular disease [7]. Adiponectin reverses insulin resistance in mouse model of lipodystrophy and obesity [8]. Thiazolidinediones (TZDs), PPAR-γ agonists, have been reported to normalize or increase adiponectin mRNA expression and secretion in adipose tissue of obese mice as well as cultured 3T3-L1 adipocytes [9]. Steppan et al. found resistin in a screen to identify potential targets of TZDs in 3T3-L1 adipocytes [10]. Administration of resistin to wild-type mice impaired glucose homeostasis and insulin sensitivity, and antibody neutralization of resistin in the diet-induced obese mice decreased blood glucose levels and improved insulin sensitivity [10]. Resistin mRNA and protein have been shown to be down-regulated by TZDs in 3T3-L1 adipocytes [11]. Although resistin originally was shown to induce insulin resistance in rodents, this adipokine has many features of pro-inflammatory cytokines in humans [7,12]. Visfatin is a novel adipokine that is produced preferentially in visceral adipose tissue of mice and humans [13]. Visfatin binds to and activates the insulin receptor, exerting insulin-mimetic effects both in vitro and in vivo [13]. Reports have shown that rosiglitazone treatment increases visfatin expression in both rats and humans [14,15]. Although both PPAR-δ and adipokines have been suggested to have an important role in insulin resistance and the metabolic syndrome [16,17], there have been no reports on the effects of PPAR-δ on adipokines.

Therefore, in the present study, we examined the effects of the PPAR-δ agonist, L-165041, on the expression of adiponectin, resistin, and visfatin in visceral adipose tissues of rats fed a high-fat diet and in 3T3-L1 adipocytes.

Materials and methods

Animals. Five-week-old male Wistar rats, weighting 170–180 g, were purchased from Japan SLC (Shizuoka, Japan). The animals were housed individually in cages with a wire-mesh bottom in rooms kept at a temperature of 20–22 °C, a humidity of 50–60%, and a 12 h-light, 12 h-dark cycle. The animals had free to access to water, as well as chow (Bethlehem, PA, USA) that contained 8.5% (w/w) fat, 43.7% carbohydrate, and 29.7% protein, and an energy content of 3.69 kcal/g; the rats were acclimated to this chow for 1 week, after which they were weighed and divided into three groups of six animals each with approximately equal mean body weights: a group fed a standard diet ($n = 6$), a group fed a high-fat diet ($n = 6$) and a group fed a high-fat diet treated with L-165041. One of the groups continued to consume standard chow, while the others were placed on a high-fat diet for 4 weeks (6–10 weeks of age). For an i.p. injection, L-165041 was dissolved in 0.5% of carboxymethyl cellulose, and rats were injected with L-165041 (10 mg/kg/day) at 09:00–10:00 for 2 weeks at the end of the experimental period. The high-fat diet, obtained from Research Diets (Bethlehem, PA, USA), contained 45% fat, 35% carbohydrate, and 20% protein. The standard diet contained 35% fat, 47% carbohydrate, and 18% protein. The animals were weighed once a week. At the end of the study period (10 weeks), animals were sacrificed and their visceral adipose tissue harvested and immediately frozen in liquid nitrogen and stored at −70 °C until their RNA was extracted. All experiments were conducted in accordance with the Korea University Guidelines for the Care and Use of Experimental Animals. We certify that all applicable institutional and governmental regulations concerning the ethical use of animals were followed during this research.

Analysis of blood samples. Blood was collected from the tail vein between 10:00 A.M. and noon under non-fasting conditions during the experimental period. All serum samples were stored at −70 °C until analysis. Serum total cholesterol, triglycerides and HDL cholesterol were determined enzymatically using a chemistry analyzer (Bayer Corp., Elkhart, USA). Free fatty acids (FFAs) levels were measured using the ACS-ACOD enzymatic method (NEFA ZYME-S, Hitachi, Japan). A glucose oxidase method was employed to measure plasma glucose, and a rat-specific RIA kit (Linco Research Inc., St. Charles, USA) was used to measure insulin levels.

Culture of 3T3-L1 cells. Murine 3T3-L1 preadipocytes were plated and grown to two days post-confluence in six well culture plates in DMEM containing 10% fetal bovine serum (FBS); the medium was changed every two days. Cells were induced to differentiate by replacing the medium with serum-containing DMEM containing 0.5 mM of methyl-3-isobutylxantine (IBMX), 0.25 μM dexamethasone (DEX), and 1 μg/ml insulin. Two days later, the medium was again changed to serum-containing DMEM that contained insulin but no IBMX or DEX. Two days later, the medium was again changed to the original DMEM containing 10% FBS in the absence of any differentiating reagents, and was replaced every two days from that day forward. In order to investigate the effects of L-165041 on the expression of various genes, the cells were treated with L-165041 (10^{-6} M) during their differentiation.

RNA analysis and quantitative reverse transcription polymerase chain reaction (qRT-PCR). Total RNA was extracted from pooled adipose tissues and 3T3-L1 adipocytes using the TRIzol reagent (Invitrogen, Calsbard, CA, USA) according to the manufacturer's instructions. Double-stranded cDNA was synthesized using a cDNA synthesis kit (Superscript Double-Stranded cDNA Synthesis kit, Invitrogen, Calsbard, CA, USA). The expression levels of the adipocytokines in 3T3-L1 adipocytes were analyzed by quantitative real time reverse transcription polymerase chain reaction (qRTRT-PCR). TaqMan probes for visfatin (Mm00451938_m1), adiponectin (Mm00456425_ml), resistin (Mm00445641_m1) PPAR-δ (Mm01305434_m1), and β-actin (Mm00607939_s1) were Assay-on-Demand gene expression products (Applied Biosystems, Foster City, CA, USA). All results were obtained in at least five independent experiments. The mRNA levels of all genes were corrected using the transcription level of the β-actin gene as an internal standard.

The expression levels of adipokines in visceral adipose tissues of 10-week-old rats were also analyzed by Semi-quantitative RT-PCR (SqRT-PCR). SqRT-PCR was performed in order to measure the levels of visfatin, adiponectin, resistin, PPAR-δ, and β-actin mRNA. The following primer sequences were used for the analysis: visfatin, 5′-gggaaagaccatg agaaaga-3′ (forward), 5′-aaggccattggttacaacat-3′ (reverse); adiponectin, 5′-ggagagaagggagagaaagg-3′ (forward), 5′-tccttcttgaagaggctcac-3′ (reverse); resistin, 5′-cctccttttccttttcttcc-3′ (forward), 5′-aggagactgtccagcaa ttt-3′ (reverse); PPAR-δ, 5′-aaccgcaacaagtgtcagta-3′ (forward) 5′-ccatactt gaggagggtcac-3′ (reverse); β-actin, 5′-aggtcatcactattggcaac-3′ (forward), 5′-actcatcgtactcctgcttG-3′ (reverse). To determine the cycle numbers that would correspond to the amplification range of all PCR products, PCR was performed from 20 to 38 cycles on cDNA generated from a single RT reaction. We performed PCR for 32 cycles with a 56 °C annealing temperature for adiponectin (product size of 350 bp), 38 cycles with a 53 °C annealing temperature for resistin (product size of 159 bp), 31 cycles with a 51 °C annealing temperature for visfatin (product size of 468 bp), 34 cycles with a 55 °C annealing temperature for PPAR-δ (product size of 494 bp) and 28 cycles with a 55 °C annealing temperature for β-actin (product size of 363 bp). Thus, all subsequent amplifications were performed using 25–38 cycles in the linear increasing phase of the PCR product. Similar results were obtained from at least three independent experiments. The mRNA levels of all genes were standardized to the transcription level of the β-actin gene used as an internal standard. PCR products were resolved on a 1.2% agarose gel. The DNA was visualized by ethidium bromide staining and analyzed using NIH image software.

Statistical analyses. All analyses were performed using SPSS for Windows statistical program (Version 10.0; SPSS, Inc., Chicago, IL, USA). Results are presented as the percentage of control values

Table 1
Effects of PPAR-δ agonist, L-165041, on the serum insulin, glucose, and lipid concentrations in rats at 10 weeks of age

	Lean	High fat	High fat + L-165041
Glucose (mmol/l)	8.86 ± 0.39^{a}	9.98 ± 0.62^{b}	9.57 ± 0.62^{b}
Insulin (pmol/l)	2.57 ± 0.76^{a}	5.63 ± 0.76^{b}	5.14 ± 1.04^{b}
Triglyceride (mmol/l)	0.62 ± 0.08	0.78 ± 0.16	0.70 ± 0.10
Total cholesterol (mmol/dl)	1.34 ± 0.07^{a}	1.53 ± 0.03^{b}	1.44 ± 0.06^{c}
HDL-cholesterol (mmol/l)	0.86 ± 0.03^{a}	0.71 ± 0.03^{b}	0.83 ± 0.11^{a}
Free fatty acids (μEq/l)	738.5 ± 22.5	748.0 ± 26.5	732.0 ± 26.1

The data represent means ± SDM.
[a,b,c] Different letters represent significant differences ($P < 0.05$).

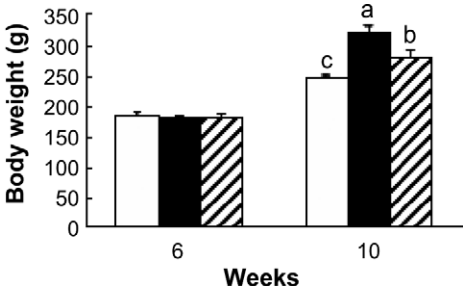

Fig. 1. Effects of PPAR-δ agonist, L-165041, on body weight in rats at 10 weeks of age. Body weights were measured at the end of the treatment period. The rats were divided into three groups: rats fed a standard diet (open bars), rats fed a high-fat diet (solid bars) and rats fed a high-fat diet treated with L-165041 (hatched bars). The data are means ± SDM from 6 rats/groups. [a,b,c]Different letters within each week represent significant differences ($P < 0.05$).

(mean ± SDM) and represent data collected from at least three experiments. Data were compared using Student's *t*-test except for those in Table 1 and Fig. 1, which were assessed using Duncan's multiple comparison tests following a one-way ANOVA.

Results

Changes of body weight

As shown in Fig. 1, rats fed a high-fat diet at 10 weeks of age showed a greater increase in body weight than those fed a standard diet ($P < 0.05$). Interestingly, the body weight gain in L-165041-treated rats was significantly ($P < 0.05$) decreased compared to that of rats fed high-fat diet.

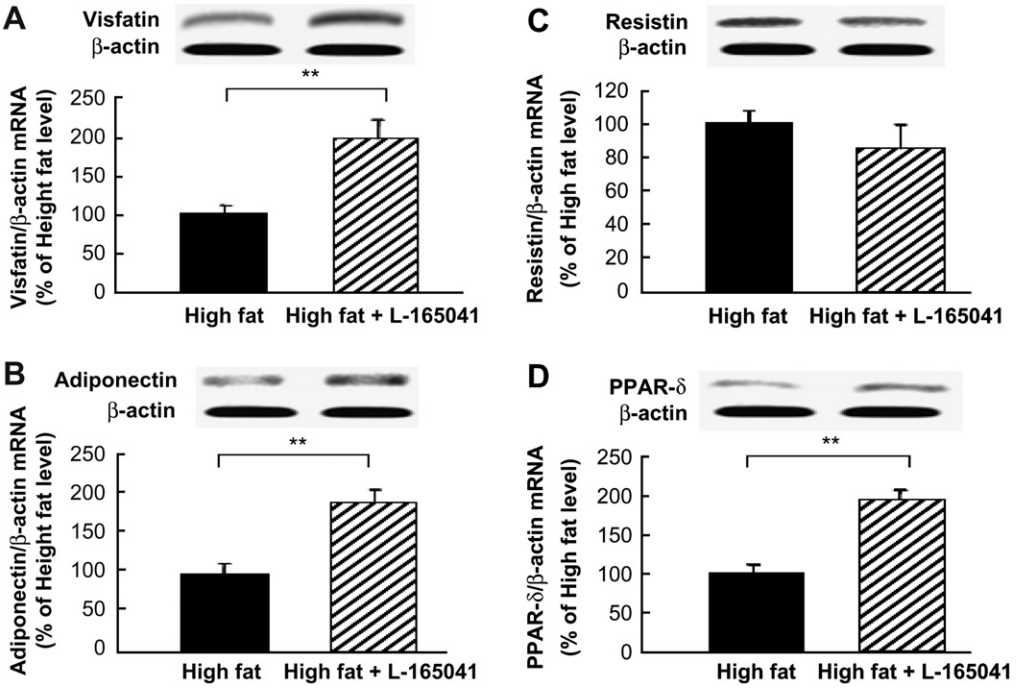

Fig. 2. Effects of PPAR-δ agonist, L-165041, on the expression of genes in visceral adipose tissue of rats. RT-PCR analysis was performed on total RNA extracted from visceral adipose tissues of 10-week-old male rats fed high-fat diet (solid bars) and high-fat diet treated with L-165041 (hatched bars). The expression levels of the genes were measured by semi-quantitative RT-PCR. Upper panel: representative ethidium bromide-stained agarose gel showing amplified visfatin (A) adiponectin (B), resistin (C), PPAR-δ (D), and β-actin. Lower panel: data were normalized using β-actin mRNA and expressed as percentages of the basal rate of 100% in rats fed high-fat diet. The data represent means ± SDM of the five experiments. PPAR-δ agonist caused a significant difference compared with the high fat-fed group. $^{**}P < 0.01$ vs. high-fat diet-fed rats.

Effects of PPAR-δ agonist on serum insulin, glucose and lipid concentrations

The concentration of serum glucose, insulin, and triglyceride slightly decreased in L-165041-treated rats, when compared to rats fed high-fat diet, although this decrease was not significant (Table 1). Furthermore, the concentration of total cholesterol was lower and HDL cholesterol was higher ($P < 0.05$) than in those rats fed a high-fat diet. In addition, L-165041 treatment induced a decrease of free fatty acid in serum, when compared to high-fat diet treatment, although this decrease was not significant.

Effect of PPAR-δ agonist on the expression of adipokine genes in visceral adipose tissue of rats

Visceral adipose tissue was isolated for analysis from 10-week-old rats that had been fed a high-fat diet and a high-fat diet treated with L-165041. We examined the expression levels for various adipokine genes in L-165041-treated rats and in untreated rats. As shown in Fig. 2, visfatin and adiponectin mRNA levels significantly ($P < 0.05$) increased in L-165041-treated rats when compared to untreated rats. However, resistin mRNA decreased in L-165041-treated rats. In addition, we confirmed that there was a significant ($P < 0.05$) increase in PPAR-δ mRNA levels with L-165041 treatment.

Effect of PPAR-δ agonist on the expression of adipokine genes in differentiated 3T3-L1 adipocytes

To investigate the expression levels of various genes during the process of differentiation of preadipocytes, L-165041 was added to the differentiation medium of preadipocytes. At day nine, the differentiation rate peaked to greater than 75%. The level of visfatin and adiponectin mRNA was up-regulated in response to L-165041 treatment over nine days. By contrast, resistin mRNA levels were down-regulated by treatment with L-165041 (Fig. 3). Levels of PPAR-δ mRNA were also increased by L-165041 during differentiation of 3T3-L1 cells.

Discussion

The present study provides novel evidence that the PPAR-δ agonist is involved in the control of the expression of various adipokines in both adipose tissues of rats fed a high-fat diet and cultured 3T3-L1 adipocyte.

PPARs are members of the nuclear receptor superfamily of ligand-inducible transcription factors. Among three isotypes of PPARs, PPAR-α, and PPAR-γ are therapeutic targets for hypertriglyceridemia and insulin resistance, respectively. Recent studies have shown that PPAR-δ enhances fatty acid catabolism and energy uncoupling in adipose tissue and muscle, as well as suppression of

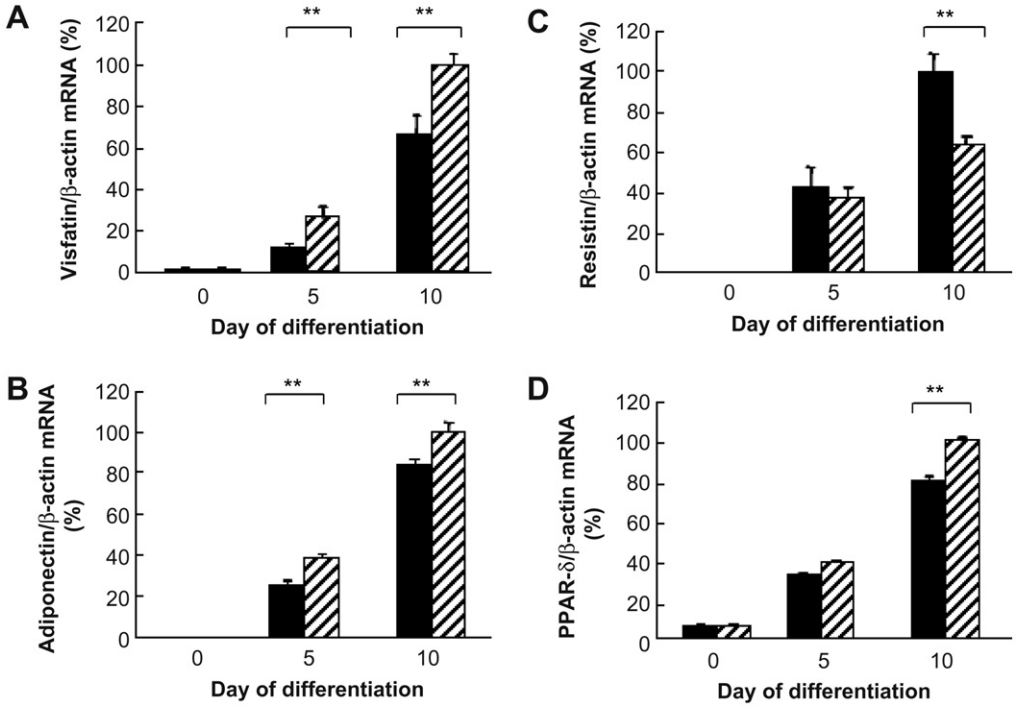

Fig. 3. Effects of PPAR-δ agonist, L-165041, on the expression levels of the genes in 3T3-L1 adipocytes. RT-PCR analysis was performed on total RNA extracted from 3T3-L1 adipocytes treated with (hatched bars) or without L-165041 (solid bars). Visfatin (A) adiponectin (B), resistin (C), and PPAR-δ (D) mRNA levels in 3T3-L1 cells treated with (+) or without (−) PPAR-δ agonist (10^{-6} M) during their differentiation. The expression levels of the genes were measured by quantitative real time RT-PCR. Data were normalized against β-actin and were expressed in percent form. The data represent means ± SEM from three independent experiments. $^{**}P < 0.01$ vs. control.

macrophage-derived inflammation [18]. However, the functional mechanisms underlying PPAR-δ activity are incompletely known to date.

Treatment of insulin-resistant obese rhesus monkeys with the PPAR-δ selective agonist GW501516 resulted in a 79% increase in HDL-C, a 56% decrease in triglycerides, and a 29% decrease in LDL cholesterol [1]. Furthermore, fasting insulin concentrations were observed to decrease, by up to 48%, in the PPAR-δ treated monkeys. Transgenic mice encoding a constitutively active viral protein 16-PPAR-δ fusion (VP16-PPAR-δ) using a gain-of-function strategy has been reported [2]. These mice exhibited decreased body weight, reduced inguinal fat mass, decreased adipocyte triglyceride accumulation and reduced circulating FFAs and triglyceride levels when compared to control mice on the same diet. In addition, up-regulation of genes involved in fatty acid oxidation, triglyceride hydrolysis and uncoupling of oxidative phosphorylation were found in these mice. Similarly, the PPAR-δ agonist GW501516 in genetically obese (*db*/*db*) mice reduced intracellular triglyceride accumulation in brown fat and the liver [2]. Furthermore, the PPAR-δ agonist prevented weight gain in models of high-fat diet-induced obesity [3]. Therefore, PPAR-δ is suggested as a therapeutic target for the metabolic syndrome with the potential to control weight gain, improve insulin sensitivity and ameliorate atherosclerosis [5]. In the present study, we found that the PPAR-δ agonist prevented weight gain in rats fed a high-fat diet. Furthermore, serum glucose, insulin, total cholesterol, triglyceride and FFAs levels showed a tendency to be lower in PPAR-δ agonist treated rats.

Adiponectin is an adipokine that is specifically and abundantly expressed in adipose tissue. Hypoadiponectinemia appears to play an important role in insulin resistance, type 2 diabetes and the metabolic syndrome [8]. In addition, adiponectin is decreased in obesity, and increase in response to weight reduction [19]. Adiponectin was observed to decrease insulin resistance by stimulating fatty acid oxidation and reducing triglyceride content in muscle and liver [20]. Plasma adiponectin levels have been shown to be up-regulated by the PPAR-γ agonist TZDs [20]. In the present study, we found that the PPAR-δ agonist increased the expression of adiponectin in both visceral fat of rats fed a high-fat diet and cultured 3T3-L1 adipocytes. These effects might provide some insight into the probable mechanism underlying the PPAR-δ agonist effect on components of the metabolic syndrome; this is because adiponectin is regarded as a possible target for the prevention and treatment of the metabolic syndrome [21].

Resistin has been identified as an adipokine that is down-regulated by TZDs. Furthermore, recombinant resistin treatment has been shown to induce insulin resistance in mice, which was improved by anti-resistin antibodies. However, following studies have shown conflicting results, and the role of resistin remain unclear in human disease [22]. Recent research has demonstrated that resistin inhibits adipocyte differentiation as a feedback regulator of adipogenesis [23]. It also has been shown to function as a regulator of glucose homeostasis as well as a physiologic antagonist of hepatic insulin action [24]. In both adipose tissues of rats fed a high-fat diet and in cultured adipocytes, PPAR-δ agonist treatment decreased resistin expression in the present study.

Visfatin is a recently identified adipokine produced and secreted primarily by visceral adipose tissue [13]. Adipocyte visfatin expression and plasma concentrations have been shown to increase with obesity in animals [13] and in humans [25]. Although visfatin function is not currently understood, visfatin may have a dual role: an autocrine/paracrine function which facilitates differentiation and fat deposition on visceral adipose tissue, and an endocrine role that modulates insulin sensitivity in peripheral organs [26]. In the present study, we found that the PPAR-δ agonist increased visfatin expression in both adipose tissues of rats fed a high-fat diet and in cultured adipocytes.

In conclusion, the present study demonstrated that PPAR-δ agonist treatment prevented weight gain, and decreased levels of serum glucose, insulin and lipids in rats fed a high-fat diet. Furthermore, the PPAR-δ agonist increased expression of visfatin, adiponectin, and decreased resistin expression in both rats fed a high-fat diet and cultured 3T3-L1 adipocytes.

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