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Chin J Clin Pharmacol Ther
Chinese Pharmacological Society
CN 34-1206/R, ISSN 1009-2501
E-mail: cept96@21cn.com
Oct; 12(10): 1157—1162

Differential effects of PPARγ ligand rosiglitazone and selective antagonist GW9662 on adipocytokine gene expression in 3T3-L1 adipocytes

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ABSTRACT **BACKGROUND**: There is a growing recognition that the adipose tissue is an endocrine organ that secretes signaling molecules such as adiponectin and resistin. The peroxisome proliferator activated receptor γ (PPARγ) is expressed in high levels in the adipose tissue. Thiazolidinediones are selective PPARγ agonists with insulin-sensitizing properties. It has been postulated that thiazolidinediones such as rosiglitazone exert their pharmacodynamic effects in part through modulation of resistin (implicated in insulin resistance) and adiponectin (an insulin-sensitizing molecule) expression subsequent to activation of PPARγ. There are conflicting data, however, on the biological direction in which resistin expression is modulated by PPARγ agonists and whether an increase in adiponectin expression can occur in the face of an upregulation of resistin. **METHODS**: Using the murine 3T3-L1 adipocytes as a model, we evaluated the changes in resistin and adiponectin gene expression after vehicle, rosiglitazone (10 μmol/L, a PPARγ agonist), GW9662 (5 μmol/L, a selective PPARγ antagonist) or GW662 and rosiglitazone co-treatment. **RESULTS**: In comparison to vehicle treatment, rosiglitazone increased the average adiponectin and resistin mRNA expression by 1.66- and 1.55-fold, respectively ($P<0.05$). Importantly, GW9662 also upregulated adiponectin expression (by 1.57-fold, $P<0.05$) but did not influence resistin expression ($P>0.05$). Co-treatment with rosiglitazone and GW9662 maintained the adiponectin upregulation (1.87-fold increase from vehicle, $P<0.05$) while attenuating resistin upregulation (1.31-fold increase from vehicle, $P<0.05$) induced by rosiglitazone alone (1.55-fold increase from vehicle, $P<0.05$). **CONCLUSION**: This study presents new evidence that adiponectin transcript is upregulated with both a PPARγ agonist (rosiglitazone) and antagonist (GW9662), while GW9662 co-treatment does not block rosiglitazone-induced adiponectin upregulation. These data collectively suggest that biological mechanisms independent from PPARγ may underlie thiazolidinedione pharmacodynamics on adiponectin expression. Moreover, increased adiponectin expression by GW9662, in the absence of an upregulation of resistin expression, lends further support on the emerging clinical potential of PPARγ antagonists in treatment of insulin resistance. Decreased resistin expression may not be crucial for the insulin-sensitizing effect of rosiglitazone. These findings may serve as a foundation for future dose-ranging and time-course studies of thiazolidinedione pharmacodynamics on adipocytokine expression in human adipocytes.

KEY WORDS PPARγ; obesity; diabetes; insulin resistance; GW9662; thiazolidinediones; rosiglitazone; adipocytokine; 3T3-L1 adipocytes; gene expression

This work was supported by research grants from the National Natural Science Foundation of China, C30528026., C30672497, and by the China Medical Board of New York grants 99-697 and 01-755.

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Obesity is a well recognized risk factor for the development of insulin resistance and type 2 diabetes. The precise molecular mechanisms by which these two complex processes are linked remain elusive. Historically, the adipose tissue was conceptualized as a passive organ of energy storage. Over the last decade, a novel role of the adipose tissue as an endocrine organ playing an active role in regulation of homeostatic systems has emerged. This is significant because the adipose tissue is known to secrete a large number of signaling molecules such as TNF-α, IL-6, leptin, PAI-1, acylation-stimulating protein, SAA3, alpha1 acid glycoprotein, adiponectin and resistin which may potentially provide a mechanistic link between increased adiposity and insulin resistance[1].

Thiazolidinediones are selective ligands for peroxisome proliferator activated receptor γ (PPARγ) and are used in the treatment of type 2 diabetes to decrease insulin resistance. PPARγ is a ligand-activated transcription factor that belongs to the nuclear receptor family and plays a critical role in gene regulation, adipocyte differentiation and lipid metabolism[2]. It has been postulated that thiazolidinediones mediate part of their insulin-sensitizing pharmacodynamic effects through activation of PPARγ and a subsequent decrease in resistin, coupled with an increase in adiponectin expression[3]. Thus, resistin was proposed as a key [susceptibility] hormone linking obesity to insulin resistance and diabetes[3]. By contrast, adiponectin is thought to increase insulin sensitivity[4,5].

Although the idea that adiponectin serves as a protective factor against insulin resistance is generally supported by several studies[4-7], the significance of resistin for development of insulin resistance or in mechanism of action of PPARγ agonists (e.g., thiazolidinediones) is not uniformly accepted[7-9]. For example, Way and colleagues (2001) found that experimental obesity in rodents is associated with severely defective resistin expression[9]. Moreover, in these preclinical models, adipose tissue resistin expression increased (i.e., instead of a decrease observed by Steppan *et al.*[3]) in response to several PPARγ agonists[9]. These conflicting observations call for additional *in vitro* studies before clinical pharmacogenomic investigations with PPARγ agonists and their effects on adipocytokines can be rationalized.

As an alternative to thiazolidinediones (PPARγ agonists), it is noteworthy that PPARγ antagonists were also proposed as a combined therapeutic strategy in obesity and type 2 diabetes[10]. This concept is supported in part by genetic evidence that a decrease in PPARγ activity increases insulin sensitivity. For example, a Pro12Ala substitution in PPARγ2 (one of the two isoforms of PPARγ) is associated with low body mass and improved insulin sensitivity[11,12]. Heterozygous PPAR gamma-deficient mice were protected from the development of insulin resistance due to adipocyte hypertrophy under a high-fat diet[13]. Similarly, the newly developed PPARγ antagonists (e.g., SR-202) have been shown to yield antiobesity and antidiabetic effects in preclinical models both *in vitro* and *in vivo*[14,15]. However, it is not clear whether and to what extent the projected antidiabetic and antiobesity pharmacodynamic consequences of PPARγ antagonism are mediated by changes in resistin and adiponectin expression.

In the present study, we evaluated the changes in resistin and adiponectin gene expression in an *in vitro* model after vehicle, rosiglitazone (PPARγ agonist), GW9662 (selective PPARγ antagonist) or GW662 and rosiglitazone co-treatment of the murine 3T3-L1 adipocytes. We submit that these observations may contribute to efforts to rationalize future clinical pharmacogenomic studies on the molecular link between PPARγ activity and insulin resistance and the postulated role of PPARγ antagonists in treatment of obesity, insulin resistance and type 2 diabetes.

1 MATERIALS AND METHODS

1.1 Materials Rosiglitazone, GW9662, insulin, dexamethasone, 1-isobutyl-3-methylxanthine, DEPC were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Trypsin and Trizol RT-PCR kit were obtained from MBI Fermentas (Lithuania). Cell culture supplies were obtained from Gibco BRL Co.

1.2 Cell culture and drug treatment The 3T3-L1 adipocytes (American Type Culture Collection) were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (culture medium). At confluence, preadipocytes were cultured for 2 days in culture medium supplemented with 5 μmol/L insulin, 0.5 mmol/L isobutylmethylxanthine and 0.25 μmol/L dexamethasone. After additional 2 days in this culture medium with 5 μmol/L insulin, cells were

grown for 4 to 8 days. At the time of experiments more than 90% of the cells had accumulated fat droplets. Hence, cell used in the experiments with four different treatment groups in our study (vehicle, rosiglitazone, GW9662, and rosiglitazone/GW9662 co-treatment) came from one bottle with differentiated adipocytes. Furthermore, prior to vehicle or drug treatments, adipocytes were maintained for 6 hour in serum-free medium for synchronization. Thus, there were no differences in the cell size or fat accumulation in 3T3-L1 cells among the four treatment groups. GW9662 (5 μmol/L) and rosiglitazone (10 μmol/L) were used at standard concentrations as previously reported in the literature on *in vitro* studies of PPARγ[16]. At these concentrations, both GW9662 (5 μmol/L) and rosiglitazone (10 μmol/L) are above their affinity constant for PPARγ (K_i=13 nmol/L and 110 nmol/L, respectively) thereby eliminating the possibility of a floor effect due to an inactive pharmacological dose[17].

1.3 Analysis of adiponectin and resistin gene expression Measurement of adiponectin and resistin gene expression was performed by semiquantitative analysis as previously described[18,19]. All experiments were performed in triplicates. In brief, total RNA was isolated from 3T3-L1 adipocytes using Trizol reagent and 1 μg of total RNA was reverse transcribed using standard reagents. 10% of each RT reaction was amplified in a 20 μL PCR reaction system. PCR condition was a denaturating step at 94 ℃ for 30 s followed by 40 cycle of 95 ℃, 1 s; 60 ℃, 7 s; 72 ℃, 10 s and a terminal extension for 7 minutes at 72 ℃. The following oligonucleotide primers were used: adiponectin: AAGGACAAGGCCGTTCTCT and TATGGGTAGTTGCAGTCAGTT-GG (antisense); resistin: CCAGCATGCCACTGTGT (sense) GTAGAGACCGGAG GACATCA (antisense); β-actin: CCAGGGTGTGATGGTGGGAATG (sense) and CGCACGATTTCCCTCTCAGCTG (antisense). PCR reaction products were transferred on a 2% TAE-agarose gel, stained with ethidium bromide and were analysed using the ImageTool software.

1.4 Statistical analysis Differences among groups were tested with one-way analysis of variance (ANOVA). Data were presented as mean ±SD. A P value less than 0.05 was set as the statistical significance threshold in all analyses.

2 RESULTS

2.1 Effects of rosiglitazone and GW9662 on adiponectin mRNA After the adipocytes were treated with vehicle, 10 μmol/L rosiglitazone, 5 μmol/L GW9662, or both 10 μmol/L rosiglitazone and 5 μmol/L GW9662 for 24 hours, the average normalized values for the adiponectin mRNA in cells were 0.47±0.11, 0.78±0.09, 0.74±0.11 and 0.88±0.23, respectively (Fig 1). All of the treatment groups showed a significant difference from the vehicle group, but not between different active drug treatment groups (Fig 1).

2.2 Effects of rosiglitazone and GW9662 on resistin mRNA The average normalized values for the resistin mRNA in adipocytes after treatment with vehicle, 10 μmol/L rosiglitazone, 5 μmol/L GW9662, or both 10 μmol/L rosiglitazone and 5 μmol/L GW9662 for 24 hours, were 0.49±0.09, 0.76±0.07, 0.61±0.10, 0.64±0.13 (Fig 2). Rosiglitazone treatment and rosiglitazone/GW9662 co-treatment resulted in a significant increase in resistin expression (P<0.05). On the other hand, there was no significant difference between GW9662 and vehicle treatment (P>0.05). Resistin upregulation by rosiglitazone was attenuated in the presence of GW9662 (1.31-fold increase from vehicle, P<0.05) compared to rosiglitazone treatment alone (1.55-fold increase from vehicle, P<0.05).

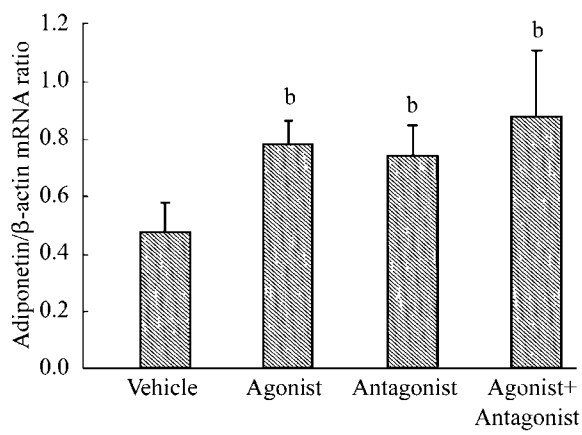

Fig 1 Pharmacodynamic effects of rosiglitazone and GW9662 on adiponectin mRNA expression. The 3T3-L1 adipocytes were treated with vehicle, 10 μmol/L rosiglitazone, 5 μmol/L GW9662, or both 10 μmol/L rosiglitazone and 5 μmol/L GW9662 for 24 hours

^bP<0.05 denotes a significant difference from the control (vehicle) treated group.

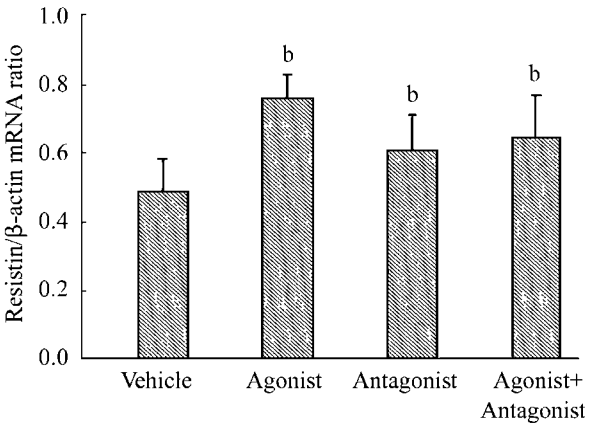

Fig 2 Pharmacodynamic effects of rosiglitazone and GW9662 on resistin mRNA expression. The 3T3-L1 adipocytes were treated with vehicle, 10 μmol/L rosiglitazone, 5 μmol/L GW9662, or both 10 μmol/L rosiglitazone and 5 μmol/L GW9662 for 24 hours

[b] $P<0.05$ denote a significant difference from the control (vehicle) treated group

3 DISCUSSION

The present study provides new supporting evidence in a cell culture model that PPARγ agonist rosiglitazone causes a significant 1.66- and 1.55-fold increase in average adiponectin and resistin mRNA expression, respectively (Figs 1 and 2). An earlier report by Steppan *et al*. has postulated that (a) elevated levels of resistin promotes insulin resistance and (b) PPARγ agonist treatment is associated with a decrease in resistin expression[3]. However, our results are consistent with reports[7-9] subsequent to that by Steppan *et al*[3]. observing an effect on resistin expression in the opposite direction (i.e., an increase) after treatment with PPARγ agonist thiazolidinediones, and reduced resistin expression in experimental models of obesity. Importantly, insulin treatment also induces resistin expression[8]. Hence, studies with both insulin itself[8] and insulin sensitizers as well as accumulation of evidence from gene expression studies in adipose tissue in obesity[7-9] are in accordance with present results with rosiglitazone, suggesting an increase in resistin and adiponectin expression by PPARγ agonist treatment.

Despite the conflicting evidence on resistin and its biological significance as a putative molecular link between obesity and insulin resistance, studies to date generally support the view that adiponectin is an important modulator of insulin sensitivity. Moreover, our study and reports by others[7-9] indicate that insulin sensitizing effects of thiazolidinediones can be mediated through an increase in adiponectin expression despite an accompanying elevation in resistin expression. Modulation of adiponectin levels complements other mechanisms by which thiazolidinediones achieve antidiabetic effects in obese individuals, for example, promotion of fat accumulation in the subcutaneous adipose tissue rather than in the visceral adipose tissue[20].

Together with its heterodimeric partner retinoid X receptor (RXR), PPARγ binds to specific peroxisome proliferator response elements (PPREs) to regulate transcription of target genes. Because PPREs were not found in the promoter regions of the adiponectin gene, it has been postulated that PPARγ agonists may induce adiponectin expression by a direct effect on its promoter and/or by antagonizing the suppressing effect of TNF-alpha on the adiponectin promoter[4]. In our study, we found that the selective PPARγ antagonist GW9662 did not reverse the upregulation of adiponectin by rosiglitazone. Moreover, an unexpected new observation in our study was that GW9662 treatment increased adiponectin expression (Fig 1), further suggesting the significance of mechanisms independent from activation or antagonism of PPARγ. Presumably, this may be explained by a direct effect of GW9662 on adiponectin promoter as also suggested for rosiglitazone above.

GW9662 did not significantly affect resistin expression, in contrast to rosiglitazone (Fig 2). From a drug development standpoint, an increase in adiponectin expression by GW9662 in the absence of upregulation of resistin levels (notwithstanding uncertainties on whether resistin confers insulin resistance or not) may prove to be advantageous. At present, the mechanism of GW9662-induced adiponectin upregulation remains unclear although it coincides with the emerging concept that PPARγ antagonists may offer therapeutic value in insulin resistance[10]. PPARγ antagonists such as SR-202 reduce TNF-alpha levels, presumably through inhibition of adipocyte differentiation[10]. Because TNF-alpha exerts an inhibitory effect on adiponectin expression, PPARγ antagonists, e.g., GW9662 can potentially release TNF-alpha-mediated suppression on adiponectin promotor[10,20]. Additionally, it is notable that trypsin digestion of the human PPARgamma/GW9662 complex reveals a pattern of digestion distinct from that with rosiglitazone. This suggests that the binding characteristics of PPARγ with GW9662

and rosiglitazone may differ or alternatively, there may be additional binding sites for GW9662 on PPARγ[17]. Further molecular studies are needed to answer these questions. Nevertheless, we indicate that an increase in adiponectin expression by GW9662 observed in our study lends evidence for the clinical potential of PPARγ antagonists in patients with both obesity and type 2 diabetes. Insulin sensitivity associated with genetically determined decrease in PPARγ activity provides further support in this regard[11, 12].

In conclusion, this study presents new evidence that adiponectin is upregulated during treatment with both a PPARγ agonist (rosiglitazone) and antagonist (GW9662). This suggests that biological mechanisms independent from PPARγ may underlie pharmacodynamic effects of rosiglitazone and GW9662 on adiponectin gene expression. Importantly, GW9662 appears to increase adiponectin expression, without markedly influencing resistin expression, thereby further reaffirming the clinical potential of PPARγ antagonists in treatment of patients with insulin resistance, obesity and type 2 diabetes. With rosiglitazone treatment, an increase in resistin expression ostensibly may occur in the face of adiponectin upregulation. Hence, resistin (downregulation) may not be the most crucial element mediating the insulin-sensitizing effects of rosiglitazone. Further translational research[21] is required, however, in order to extend our observations in the present *in vitro* model to human adipocytes using both mRNA and protein expression analysis. These future studies should also pay attention to characterizing dose-response and time-course relationships after treatment with PPARγ agonists and antagonists as well as coordinate effects of adipocytokines and other key molecules of insulin resistance and fat synthesis such as TNF-α, IL-6, leptin, SCD-1 and SREBP-1[1, 22].

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PPARγ 配体罗格列酮及其激动剂 GW9662 对脂肪细胞因子表达的影响

摘要　目的: 脂肪组织是一个内分泌器官已逐渐得到了肯定, 它能分泌多种信号分子如: 脂联素和抵抗素。过氧化物酶体增殖物激活受体(peroxisome proliferator activated receptor γ, PPARγ)在脂肪组织高水平表达, 胰岛素增敏剂—噻唑烷二酮类药物是它的选择性激动剂, 噻唑烷二酮类药物如罗格列酮的胰岛素增敏作用部分是通过激活 PPARγ 调节脂联素(胰岛素增敏分子)和抵抗素(涉及胰岛素抵抗)表达介导的。但现在不同研究发现 PPARγ 激动剂对抵抗素的表达调控方向存在矛盾, 我们的问题是当抵抗素表达增加的情况下脂联素的表达还能否上调。方法: 用 3T3-L1 细胞株作为研究模型, 分别用溶媒对照、罗格列酮(10 μmol/L)、GW9662(5 μmol/L)或罗格列酮＋GW9662 作用细胞, 然后检测脂联素和抵抗素 mRNA 表达变化情况。结果: 与对照组相比, 罗格列酮分别增加脂联素和抵抗素 mRNA 水平 1.77 和 1.66 倍, 其差异具有统计学意义($P<0.05$); 重要的是GW9662 也增加脂联素水平(1.57 倍, $P<0.05$)但对抵抗素无影响。罗格列酮和 GW9662 两者合用时, 仍上调 adiponectin mRNA 水平(对照组的 1.87 倍, $P<0.05$), 抵抗素的增加与罗格列酮单用比弱下降(对照组的 1.31 倍, $P<0.05$)。结论: 本研究为 PPARγ 激动剂(罗格列酮)和拮抗剂(GW9662)都上调脂联素的转录提供了新的证据, 两者合用时 GW9662 不阻断罗格列酮诱导的脂联素上调作用。综合这些数据提示噻唑烷二酮类药上调脂联素的机制可能不依赖于 PPARγ。并且, GW9662 在增加脂联素水平的同时不上调抵抗素水平的特性进一步支持 PPARγ 拮抗剂用于临床治疗胰岛素抵抗的可能性。降低抵抗素表达可能不是罗格列酮胰岛素增敏作用的重要机制。我们的结果为将来研究噻唑烷二酮类药物对人脂肪细胞因子表达在剂量和时间上提供了一定的基础。

关键词　过氧化物酶体增殖物激活受体; 罗格列酮; GW9662; 脂联素; 抵抗素