Insulin-Mediated Upregulation of the Renin Angiotensin System in Human Subcutaneous Adipocytes Is Reduced by Rosiglitazone

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Background—Obesity-associated hypertension is likely to be due to multiple mechanisms. Identification of the renin-angiotensin system (RAS) within adipose tissue does, however, suggest a potential causal role for it in obesity-associated hypertension. Obese patients are often hyperinsulinemic, but mechanisms underlying insulin upregulation of the RAS in adipose tissue are unclear. Tumor necrosis factor-α (TNF-α), an inducer of angiotensinogen in hepatocytes, is elevated in hyperinsulinemic, obese individuals and may provide a link in mediating insulin upregulation of the RAS in adipose tissue. Furthermore, thiazolidinediones lower blood pressure in vivo, and downregulation of the RAS in adipose tissue may contribute to this effect. We therefore examined the effect of rosiglitazone (RSG) on the insulin-mediated upregulation of the RAS.

Methods and Results—Sera were obtained from the arterial circulation and from venous blood by draining subcutaneous abdominal adipose tissue. Isolated human abdominal subcutaneous adipocytes (n=12) were treated with insulin (1 to 1000 nmol/L), insulin in combination with RSG (10 nmol/L), and RSG (10 nmol/L) alone to determine angiotensinogen expression and angiotensin II, bradykinin, and TNF-α secretion. Subcutaneous adipocytes were also treated with TNF-α (10 to 100 ng/mL) to examine the direct effect on angiotensinogen expression and angiotensin II secretion. The findings showed that the arteriovenous difference in angiotensin II levels was significant (23%; P<0.001). Insulin increased TNF-α secretion in a concentration-dependent manner (P<0.01), whereas RSG (10 nmol/L) significantly reduced the insulin-mediated rise in TNF-α (P<0.001), as well as angiotensin and angiotensin II. TNF-α also increased angiotensinogen and angiotensin II in isolated adipocytes.

Conclusions—The present in vivo data suggest that human subcutaneous adipose tissue is a significant source of angiotensin II. This study also demonstrates a potential TNF-α–mediated mechanism through which insulin may stimulate the RAS and may contribute to explain obesity-associated hypertension. RSG downregulates the RAS in subcutaneous adipose tissue, and this effect may contribute to the long-term effect of RSG on blood pressure. (Circulation. 2005;111:1954-1961.)

Key Words: obesity hypertension angiotensin

Hypertension is a heterogeneous condition that is linked positively with obesity, although the causative factors for this association remain unclear.1 Although the identification of the renin-angiotensin system (RAS) has been documented within several tissues, its presence in human adipose tissue may offer a potential link between obesity and hypertension.2 Thus, RAS activation through the effector hormone angiotensin II (Ang II) may alter vasoconstrictive and prothrombotic properties associated with cardiovascular disease.3-6

We have previously shown that insulin upregulates the RAS system in human adipose tissue, but the underlying mechanism for it was not clear.7 Tumor necrosis factor-α (TNF-α) is implicated in the development of insulin resistance because of the multitude of effects it exerts on insulin-sensitive tissues. Numerous studies have demonstrated a positive correlation between TNF-α and obesity with regard to protein and mRNA expression in adipose tissue, as well as circulating levels of TNF-α in obese subjects and subjects with type 2 diabetes mellitus.8,9 Furthermore, an association between elevated TNF-α expression in adipose tissue and characteristics of insulin resistance has been described in obese and diabetic animal models, as well as in humans.8,10 TNF-α can also regulate expression of angiotensinogen.
(AGT) in hepatocytes because the AGT promoter contains a cytokine-inducible enhancer known as the acute-phase response element.\textsuperscript{11} TNF-\(\alpha\) induces transcription of AGT via the transcription factor nuclear factor-\(\kappa\)B, which is known to be involved in the production of numerous proinflammatory markers. This suggests a possible TNF-\(\alpha\)-directed mechanism through which insulin may increase AGT and subsequent Ang II secretion.

Therefore, the aim of the present study was to investigate the importance of the RAS in the pathogenesis of obesity-associated hypertension both in vivo and in vitro. First, we established the importance of subcutaneous abdominal adipose tissue as a source of circulating Ang II and TNF-\(\alpha\) using an arteriovenous approach. Because our previous studies had shown that insulin increases expression of the RAS, we examined the effect of insulin on the secretion of bradykinin to determine the net effect of insulin on the RAS pathway, thus delineating the potential hypertensive effect of insulin to determine the net effect of insulin on the RAS pathway, thus delineating the potential hypertensive effect of insulin. Furthermore, we investigated whether insulin was regulating AGT through a TNF-\(\alpha\)-directed mechanism by examining the effect of insulin and RSG on the secretion of TNF-\(\alpha\) from mature adipocytes. We then proceeded to determine the effect of TNF-\(\alpha\) on AGT protein expression and Ang II secretion, to elucidate a potential pathway for insulin leading to obesity-associated hypertension through its effects on adipose tissue. Lastly, because the insulin sensitizer rosiglitazone (RSG) has been shown to lower blood pressure in animal models, patients with impaired glucose tolerance, patients with type 2 diabetes mellitus, and nondiabetic hypertensive individuals,\textsuperscript{12–16} we investigated the effect of RSG on AGT expression and Ang II secretion in human adipocytes.

**Methods**

**Subjects**  
Serum samples were obtained from consenting white, nondiabetic female subjects (age 42.3±16 years [mean±SD]; body mass index [BMI] 29.8±5.4 kg/m\(^2\) [mean±SD]; n=26). Arteriovenous difference studies were undertaken on 18 of the subjects. All subjects were weight-stable for at least 2 months before the study and were considered to be in good health after they completed a comprehensive medical evaluation that included history and physical examination, blood tests, and ECG. No subjects were taking regular medication regularly before the study. The East London Research Ethics Committee approved the study, and all subjects gave informed written consent before their participation.

For the purposes of tissue culture, subcutaneous abdominal adipose tissue was obtained from a separate cohort of female subjects (age 49.1±9.7 years; BMI 24.96±0.70 kg/m\(^2\); n=12). All human adipose tissue was obtained through elective surgery in accordance with guidelines of the South Birmingham ethics committee.

**In Vivo Assessment of the Release of Ang II and TNF-\(\alpha\) From Subcutaneous Abdominal Adipose Tissue Into the Circulation**  
Ang II and TNF-\(\alpha\) levels were assayed in sera obtained from the arterial circulation and directly from venous drainage of the subcutaneous abdominal adipose tissue depot, in accordance with a previously described method.\textsuperscript{17,18} These measurements were made on 18 subjects who had been requested to consume a diet that contained 70 mmol/d for at least 7 days before study. Twenty-four-hour urinary collections were done to check compliance with the sodium restriction. Subjects were admitted to the Clinical Research Centre in the evening before the study. At 6 pm, subjects ingested a meal that contained 12 kcal/kg body weight for lean subjects and 12 kcal/kg adjusted body weight for obese subjects (adjusted body weight=ideal body weight+(actual body weight−ideal body weight)×(0.25))). At 8 pm, subjects ingested a defined snack that contained 250 kcal, 44 g of carbohydrate, 6.1 g of fat, and 8.8 g of protein. After consuming this snack, all subjects fasted until completion of the study the following day.

On the morning of the study, 20-g catheters were inserted into a forearm vein for isotope infusion and into a radial artery for arterial blood sampling. An abdominal vein to drain subcutaneous abdominal adipose tissue was cannulated with a 10- to 20-cm, 22-gauge polyurethane catheter (Hydrocath, Viggo-Spectramed).\textsuperscript{17–19} Blood withdrawn from such catheters represents drainage from adipose tissue and overlying skin. All vascular catheters were kept patent by continuous saline infusion. Subjects remained supine throughout the study, and room temperature was kept constant at 23°C during the entire study. Blood samples were taken into prechilled syringes. Samples were kept on ice, and serum was separated rapidly by centrifugation at 4°C and was thereafter stored at −80°C until assay. Commercially available ELISA-based colorimetric kits were used to examine levels of Ang II and TNF-\(\alpha\) in the thawed serum samples (Phoenix Pharmaceuticals and R&D Systems, respectively).

Abdominal subcutaneous adipose tissue blood flow was evaluated by the 133Xe washout technique.\textsuperscript{16,19} A total of 40 to 50 mCi of 133Xe dissolved in 0.1 mL of saline was injected slowly over 60 seconds into the subcutaneous abdominal adipose tissue space. The decline in 133Xe was monitored continuously from 60 to 120 minutes after injection with a sodium iodide scintillation detector set to measure the 81-keV 133Xe photopeak.

**Tissue Culture**  
In brief, 10- to 20-g wet weight of fresh abdominal subcutaneous adipose tissue was collected. Tissue was washed initially with 1X Hank’s balanced salt solution containing penicillin (100 U/mL) and streptomycin (100 \(\mu\)g/mL). Visible blood vessels and connective tissue were removed, and the tissue was finely chopped. All adipose tissue was digested with the same batch of collagenase class 1 (2 mg/mL, Worthington Biochemical Corporation) in 1X Hank’s balanced salt solution (Gibco) for 1 hour at 37°C in a water bath and shaken at 100 cycles/min at 37°C.\textsuperscript{20} The disrupted tissue was filtered through a double-layered cotton mesh, and preadipocyte cells and adipocytes were separated by centrifugation at 360g for 5 minutes.

**Mature Adipocyte Isolation**  
After centrifugation, the upper layer of mature adipocytes was removed from the collagenase-dispersed preparation, washed in phenol red-free medium DMEM:F12 twice, and centrifuged at 360g for 2 minutes. Adipocytes were then cultured in flasks (25 cm\(^2\)) in phenol red-free Dulbecco’s modified Eagle medium (DMEM/F-12) medium containing glucose (15 mmol/L), penicillin (100 U/mL), and streptomycin (100 \(\mu\)g/mL). Aliquots of 1 mL containing \(\approx\)500,000 mature adipocytes were maintained in medium (5 mL per 25-cm\(^2\) flask) for 48 hours and treated once with insulin alone (1 to 100 nmol/L; Sigma), insulin in combination with RSG (insulin 1 to 1000 nmol/L and RSG 10 nmol/L), RSG alone (10 nmol/L), and TNF-\(\alpha\) (10 to 100 ng) for 48 hours. Adipocytes maintained in untreated medium for 48 hours were used as controls. After incubation of adipocytes (37°C/5%\ CO\(_2\)) with their respective treatments, the conditioned media and adipocytes were separated by centrifugation (360g for 2 minutes). The media were then removed, separated into aliquots, and stored at −70°C.

**Protein Assay**  
After removal of the conditioned media, 4% SDS was added to the adipocytes. The suspension was then heated for 2 hours at 95°C. until the adipocyte cells had dissolved. The resultant extracted proteins were stored at −70°C as described previously.\textsuperscript{21} Protein was...
extracted and quantified via the Bio-Rad DC (Detergent Compatible) protein assay kit. Adipocyte protein samples were assessed to determine that there was no significant statistical variation between control and treatment regimens, which indicates secretion of Ang II was not due to adipocyte protein variation between samples.

**Western Blotting**

Western blot analysis was performed by a method described previously. In brief, equal amounts (20 μg) of protein were loaded onto a 10% gel. After gel electrophoresis and electroblotting, filters were incubated overnight at 4°C with continual motion, with a primary antibody of 1:250 for AGT. Detection of AGT (61 kDa) and TNF-α (16 kDa) was achieved with horseradish peroxidase–conjugated secondary antibodies (CalBiochem) diluted 1:40,000 in PBS with Tween 20 (0.05% T). A chemiluminescent detection system (ECL/ECL+; Amersham) enabled visualization after exposure to radiographic film for 5 to 20 minutes. Autoradiographs were quantified by densitometry with a Gelbase/Gelblot program (UVP Ltd).

**Ang II, Bradykinin, and TNF-α Assays**

Secreted Ang II, bradykinin, and TNF-α from adipocytes were determined. For this, stored conditioned medium samples were thawed, and commercially available ELISA-based colorimetric kits were used to determine the quantities of Ang II, bradykinin, and TNF-α secreted from adipocytes (Phoenix Pharmaceuticals; Bachem, and R&D Systems, respectively).

**Statistical Analysis**

For assessment of protein expression and secretion, statistical analysis was undertaken with ANOVA for comparison of control versus treatments. The threshold for significance was $P < 0.05$. Data in the text and figures are presented as mean±SD or mean±SEM. SPSS version 12 was used to examine correlations.

For comparison of arterial and venous drainage for each subject, data were analyzed with a paired $t$ test. Correlations were determined with a Pearson correlation. All statistics were performed on SPSS version 12.

**Results**

**Subcutaneous Abdominal Adipose Tissue Production of Ang II**

In these subjects (age 43±15.3 years [mean±SD]; BMI 30.70±4.83 kg/m² [mean±SD]; insulin 8.1±3.5 μU/mL [mean±SD]; glucose: 5.3±0.9 mmol/L; systolic blood pressure 129.3±19.5 mm Hg; diastolic blood pressure 83.2±9.5 mm Hg; n=18), abdominal venous Ang II levels were significantly higher than levels in the arterial circulation. Ang II levels were 23% greater in the subcutaneous abdominal venous drainage than in the artery ($P < 0.001$; Table). The arteriovenous concentration difference across adipose tissue showed a similar trend for TNF-α, although this did not achieve statistical significance ($P < 0.083$; data not shown). The mean adipose tissue plasma flow across this depot was 1.46±0.91 mL·100 g−1·min−1. The production rate for Ang II was 54±56.68 pg/100 g adipose tissue per minute (mean±SD), whereas TNF-α was 14±26.24 pg/100 g adipose tissue per minute (mean±SD). Whole-body Ang II adipose tissue production rate was 1626±390.7 pg/mL (mean±SE).

**Correlation Between Plasma Ang II Levels and BMI**

Increasing BMI showed a positive correlation with increasing circulating Ang II levels in these subjects (age 42.3±16 years [mean±SD]; BMI 29.8±5.4 kg/m² [mean±SD]; n=26; $r^2=0.142$, $P=0.057$; Figure 1), although this was not significant. Ang II levels from subcutaneous venous drainage showed no correlation with increasing BMI (data not shown). Increasing BMI also showed a significant positive correlation with increasing diastolic blood pressure ($r^2=0.414$, $P < 0.01$; data not shown); however, no such association was observed with systolic blood pressure (data not shown).

**Correlation Between Venous Adipose Tissue TNF-α and Ang II Levels**

TNF-α and Ang II from subcutaneous adipose tissue venous drainage demonstrated a significant positive correlation with increasing levels ($r^2=0.491$, $P < 0.01$; Figure 2).

**Effect of Insulin and Insulin With RSG on Secretion of TNF-α**

In human subcutaneous adipose cells, insulin increased TNF-α secretion in a concentration-dependent manner ($P < 0.01$), whereas RSG (10 nmol/L) significantly reduced the insulin-mediated rise in TNF-α (mean±SEM: control 3.8±0.60 ng/mL; insulin 10 mol/L 5.2±0.3 pg/mL; insulin 10 nmol/L plus RSG 0.9±0.4 ng/mL; $P < 0.001$; Figure 3.). RSG alone (10 nmol/L) significantly reduced TNF-α secretion compared with control (mean±SEM: control 3.8±0.60 ng/mL; RSG 0.9±0.4 ng/mL; $P < 0.001$; data not shown).

**Effect of TNF-α on AGT Protein Expression**

Western blot analysis confirmed a concentration-dependent increase in AGT protein expression in subcutaneous adipocytes treated with increasing concentration of TNF-α com-
pared with control (mean±SEM: control 1±0.0; TNF-α 100 ng 3.7±0.5, *P*<0.001; Figure 4).

**Effect of TNF-α on Ang II Secretion**

Human subcutaneous abdominal adipocytes treated with TNF-α for 48 hours showed a concentration-dependent increase in Ang II secretion with maximal stimulation at 100 ng of TNF-α compared with control (mean±SEM: control 237.0±52; TNF-α 100 ng 398±61 pg/mL; **P**<0.05; Figure 5).

**Effect of Insulin in Combination With RSG on AGT Protein Expression**

Western blot analysis demonstrated that the presence of the insulin sensitizer RSG significantly reduced the insulin-mediated increase in AGT protein expression at all concentra-

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**Figure 1.** Relationship between circulating Ang II levels and BMI (n=26; *P*<0.057).

**Figure 2.** Relationship between subcutaneous venous drainage TNF-α and Ang II levels (n=15; **P**<0.01) as demonstrated by Pearson correlation.

**Figure 3.** TNF-α secretion (mean±SEM ng/mL) from untreated (control) and treated adipocytes, comparing effect of insulin (Ins; 1 to 1000 nmol/L) vs insulin in combination with RSG (10 nmol/L) on secretion of TNF-α in adipocyte cells over 48 hours (n=12; ***P***<0.001).
Effect of Insulin and RSG on Ang II Secretion

Ang II secretion was regulated by insulin in a concentration-dependent manner, with maximal stimulation occurring at 1000 nmol/L (Figure 7); however, in the presence of RSG, the insulin-mediated rise in Ang II secretion was reduced significantly at all insulin concentrations (P < 0.001; Figure 7). RSG alone (10 nmol/L) significantly reduced Ang II secretion compared with control (mean ± SEM: control 214.33 ± 12.34 pg/mL; RSG 104.44 ± 14.35 pg/mL; P < 0.01; data not shown).
Effect of Insulin and Insulin With RSG on Bradykinin Secretion

Subcutaneous abdominal adipocytes treated for 48 hours showed no significant change in bradykinin secretion with insulin treatment (1 to 100 nmol/L) or insulin (1 to 100 nmol/L) in combination with RSG (10 nmol/L; data not shown). RSG alone (10 nmol/L) did not alter bradykinin secretion (data not shown).

Discussion

Many studies have implicated a role for the adipose tissue RAS in the development of obesity-associated hypertension. Rodent studies comparing blood pressure levels in obese Zucker rats versus genetically lean Zucker rats have shown that blood pressure is significantly higher in the obese rodents. Furthermore, the administration of an Ang II receptor antagonist to these animals significantly lowered blood pressure, thus demonstrating that Ang II contributes to the elevated blood pressure observed in these animal models. However, studies by Faloia and colleagues did not demonstrate a difference in circulating components of the RAS between obese hypertensive subjects, obese normotensive subjects, and lean controls. The present findings indicate a positive correlation between increasing BMI and circulating Ang II levels, although this was not significant. The present study also revealed a positive association between BMI and diastolic blood pressure, whereas systolic blood pressure exhibited no correlation with BMI. These findings support the association between obesity, hyperinsulinemia, increased Ang II production, and elevated blood pressure. Furthermore, in addition to its systemic effects, recent studies have highlighted the importance of resistance vessels within adipose tissue depots with regard to hypertension. Both structural and functional abnormalities have been identified in arterial resistance vessels extracted from adipose tissue depots in patients with type 2 diabetes mellitus and hypertensive patients. Therefore, the local RAS may also be acting in a paracrine fashion to have a significant effect on blood pressure, as well as being a potential mediator in the observed vascular remodeling of these vessels.

Although the positive correlation between obesity and hypertension is apparent, the molecular mechanisms that underlie its pathogenesis remain unclear. Hypertension and hyperinsulinemia/insulin resistance form part of the diagnostic criteria for the metabolic syndrome, a condition that is strongly associated with obesity. We have previously investigated the effect of increasing insulin concentration on the RAS in subcutaneous human adipocytes and subsequently demonstrated that insulin concentration increases both expression and secretion of AGT and Ang II, respectively. These data suggested that chronic exposure to elevated insulin levels might induce upregulation of the RAS in subcutaneous adipocytes, thus proffering a potential mechanism to mediate obesity-associated hypertension. Furthermore, the importance of the RAS pathway is not limited to hypertension, because Ang II, the effector molecule in the pathway, has also been identified as a proinflammatory factor. Studies have shown that it activates expression of early-response and inflammatory genes in vascular smooth muscle cells and regulates the production of plasminogen activator inhibitor-1, which inhibits fibrinolysis. Obesity is associated with a state of subclinical inflammation, so the pluripotent nature of Ang II has implications for other facets of the condition. Therefore, understanding the mechanisms through which AGT and hence Ang II are regulated may provide additional insights into the pathogenesis of the metabolic syndrome and new approaches to reducing the risk of cardiovascular disease.

In the present study, we have demonstrated that subcutaneous adipose tissue is a significant site of AGT and angiotensin II production via arteriovenous measurements and through in vitro protein studies. Previous rodent studies have indicated the importance of adipose tissue RAS as contributing to plasma levels of AGT and Ang II, but no study to date has examined the importance of subcutaneous abdominal human adipose tissue. The present findings revealed a significant increase in Ang II levels in the subcutaneous abdominal adipose tissue effluent of 23% (P<0.001), thus affirming the relevance of studying this tissue with regard to obesity-associated hypertension.

We also determined that insulin did not influence bradykinin secretion. Consequently, the possible mechanisms through which insulin increased AGT, and hence Ang II protein secretion, were examined. A potential mechanism for regulation of adipose tissue RAS was suggested by the observation that in hepatocyte cells, the AGT promoter contains a cytokine-inducible enhancer known as the acute-phase response element. One cytokine known to induce transcription of AGT is TNF-α, a multifunctional cytokine produced by a variety of cells that include monocytes/macrophages, muscle cells, and adipose tissue. TNF-α is implicated as a pathogenic factor in the development of obesity-associated insulin resistance, because elevated levels of this cytokine in adipose tissue are associated with features of the metabolic syndrome. Therefore, we initially examined the levels of TNF-α produced by subcutaneous adipose tissue. TNF-α demonstrated a similar increase in the arterial versus venous drainage to Ang II, although this was not significant (P=0.083). This finding is in agreement with previous observations by Mohamed-Ali and coworkers but does not completely discount the importance of adipose tissue TNF-α, because levels may be lower owing to the local uptake of this cytokine. Furthermore, the present findings show that increasing TNF-α levels from venous drainage of the subcutaneous adipose tissue depot were strongly correlated with Ang II levels, thus supporting the possibility of a regulatory role for TNF-α in the RAS pathway.

To determine whether the effects of insulin on the RAS were a result of a TNF-α-mediated pathway, the effects of insulin on TNF-α secretion from human adipocytes were examined. The present study demonstrated that insulin stimulates TNF-α secretion in a concentration-dependent manner in isolated subcutaneous adipocytes, following the same trend as previously observed for Ang II with increasing insulin concentration. In addition, we further examined the direct effect of TNF-α concentration on AGT and Ang II stimulation. TNF-α stimulated both AGT expression and Ang II secretion in a concentration-dependent manner, with higher...
levels of TNF-α (100 ng) significantly stimulating Ang II. As such, the present results support a TNF-α–mediated mechanism for the induction of AGT in human adipocytes, as observed in hepatocytes. The previously described insulin-mediated increase in AGT and Ang II may therefore be a result of TNF-α activity.

Previous data have demonstrated that RSG reduces blood pressure in animal models, patients with type 2 diabetes mellitus, and obese patients. RSG has been shown to reduce oxidative stress, thus ameliorating endothelial dysfunction and improving blood vessel elasticity. However, no study to date has examined the effects of RSG on the RAS in human adipocytes and obesity-associated hypertension. The present study showed that the introduction of RSG into this system dramatically reduced the insulin-mediated effect on the RAS. This is an interesting finding, because the insulin-sensitizing action of RSG, through transactivation of responsive genes, would suggest that AGT and Ang II would increase further in the presence of this agent. These findings, however, are in accord with in vivo data, with RSG inducing downregulation of TNF-α and the RAS in adipocytes in vitro. In addition, RSG also negated the insulin-mediated increase in TNF-α secretion, which further supports the possibility of a TNF-α–regulated effect on the RAS; however, the effects of insulin and RSG were limited to the vasoconstrictive pathway in the RAS cascade, because bradykinin secretion remained unaltered by insulin in the presence of RSG.

In conclusion, exposure of adipose tissue to a hyperinsulinemic environment may produce increased Ang II through the actions of TNF-α, which is also elevated in obese and type 2 diabetic subjects. The present findings demonstrate the potential of this mechanism and the contributory role that the adipose tissue RAS may have in obesity-associated hypertension. RSG mitigates the insulin-mediated increase in the adipose tissue RAS, and therefore, this finding may help to explain the long-term antihypertensive effects of RSG. RSG has already been shown to improve endothelial dysfunction and hence may offer additional benefits in terms of the adipose tissue RAS. It remains unclear how RSG produces its effects. Within liver cells, it is apparent that the TNF-α–mediated induction of AGT involves the nuclear transcription factor nuclear factor-kB, a protein linked to the regulation of many proinflammatory cytokines. This pathway has not been examined in the adipocyte with regard to the RAS. It may be the key transcription factor involved in this pathway and therefore requires further investigation.

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Disclosure

Dr Smith is an employee of and has shareholdings in GlaxoSmithKline, the company that produces the insulin sensitizer rosiglitazone.

References


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