Divergent Effects of Peroxisome Proliferator-activated Receptor γ Agonists and Tumor Necrosis Factor α on Adipocyte ApoE Expression*

Received for publication, July 26, 2004, and in revised form, August 25, 2004
Published, JBC Papers in Press, August 31, 2004, DOI 10.1074/jbc.M408461200

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ApoE is expressed in multiple mammalian cell types in which it supports cellular differentiated function. In this report we demonstrate that apoE expression in adipocytes is regulated by factors involved in modulating systemic insulin sensitivity. Systemic treatment with pioglitazone increased systemic insulin sensitivity and increased apoE mRNA levels in adipose tissue by 2–3-fold. Treatment of cultured 3T3-L1 adipocytes with ciglitazone increased apoE mRNA levels by 2–4-fold in a dose-dependent manner and increased apoE secretion from cells. Conversely, treatment of adipocytes with tumor necrosis factor (TNF) α reduced apoE mRNA levels and apoE secretion by 60%. Neither insulin nor a peroxisome proliferator-activated receptor (PPAR) γ agonist regulated adipocyte apoE gene expression. In addition, treatment of human monocyte-derived macrophages with ciglitazone did not regulate expression of apoE. Additional analyses using reporter genes indicated that the effect of TNFα and PPARγ agonists on the apoE gene was mediated via distinct gene control elements. The TNFα effect was mediated by elements within the proximal promoter, whereas the PPARγ effect was mediated by elements within a downstream enhancer. However, the addition of TNFα substantially reduced the absolute levels of apoE reporter gene response even in the presence of ciglitazone. These results indicate for the first time that adipose tissue expression of apoE is modulated by physiologic regulators of insulin sensitivity.

Apolipoprotein E is a 35-kDa glycoprotein that circulates as a surface component of plasma lipoproteins and is expressed in multiple mammalian cell types (1–4). Reports over many years have demonstrated that apoE is involved in maintaining important aspects of organismal and cellular homeostasis. For example, disordered apoE function/expression has a well established role in the pathophysiology of important human diseases such as atherosclerosis and dementia (1–6). ApoE has also been implicated in regulating the expansion of the renal mesangial matrix, in regulating the differentiated function of steroidogenic tissues, and protecting cells from oxidant stress (7–9). In line with its diverse roles in normal mammalian physiology, apoE is expressed in multiple cell types, including vessel wall macrophages and cells of the central nervous system, in steroidogenic tissue, and in the kidney (1–9). As a surface component of lipoproteins, apoE is involved in regulating organismal lipoprotein metabolism (1–4). Hepatocytes are the predominant source of circulating apoE; however, peripheral tissues can also contribute importantly to plasma apoE levels (10, 11). Furthermore, it has been demonstrated that circulating apoE derived from peripheral cells can play an important role in modulating systemic lipoprotein metabolism and cholesterol levels (10–12). It can also modulate vessel wall atherosclerosis independent of its effects on cholesterol level. For example, in apoE knockout mice, the synthesis and secretion of apoE to the periphery leads to production of ~2% of wild-type circulating apoE levels reduced atherosclerosis by 80–95% even though there was no effect on hypercholesterolemia (11). In addition, circulating apoE has been postulated to play a role in suppressing systemic oxidant stress (13).

ApoE expression has also been demonstrated in adipocytes. Zechner et al. (14) demonstrated apoE mRNA and protein expression in 3T3-L1 adipocytes and in adipose tissue biopsies collected from the gluteal region of human subjects. In these studies, the expression of apoE was found to increase as a function of 3T3-L1 differentiation; almost no apoE was detected in preadipocytes. In addition, inhibition of adipocyte lipid accumulation by bion deprivation reduced apoE expression. Conversely, cholesterol loading of adipocytes enhanced apoE expression.

Multiple potential control elements for apoE gene expression have been described in its 5’ proximal promoter (15–19). In addition, downstream control elements have been described that are required to direct specific expression of apoE in various tissues. Two downstream duplicated enhancers have been reported that specify expression of the apoE gene in macrophages and adipocytes of transgenic animals (20). Furthermore, an LXR response element embedded within these enhancer elements has been shown to transduce the stimulatory effect of sterol/oxysterol on apoE gene expression in macrophages and adipocytes (21, 22).

Adipocytes are a major cell target for PPARγ agonists (23). This class of compounds includes two drugs, pioglitazone and rosiglitazone, that are widely used to treat patients with diabetes. In view of the widespread use of these drugs in human patients, the important role for PPARγ in modulating adipocyte apoE expression has been investigated in the present study.

* This work was supported by National Institutes of Health Grant HL 39653 (to T. M.), a Merit Review Grant from the Veterans Administration, a grant from the American Diabetes Association, an investigator-initiated grant from Takeda Pharmaceuticals, General Clinical Research Center Grant M01RR14288, and National Institutes of Health Grant DK 39176 (to P. A. K.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1744 solely to indicate this fact.

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¶ The abbreviations used are: LXR, liver x receptor; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor; RT, reverse transcription.
cyte function, the observation that apoE is made in adipocytes, and the important and diverse roles that have been ascribed to apoE in organismal homeostasis, we evaluated a role for PPARy agonists in regulating adipocyte apoE expression. We demonstrate that ciglitazone and pioglitazone increase adipocyte apoE expression. Furthermore, we show that TNFα markedly suppresses apoE expression in adipocytes.

**EXPERIMENTAL PROCEDURES**

**Materials**—Cell culture media, supplements, and antibiotics were purchased from Invitrogen. Ciglitazone, insulin, dexamethasone, methylisobutylxanthine, methyalosubutylxanthine, and Hanks’-buffered saline were from Sigma. W3/14643 was purchased from Biomol Research Laboratories. TNFα, IFN-γ, GM-CSF, and IL-1β were from R&D systems. All other chemicals and reagents were purchased from Sigma-Aldrich.

**Cell Culture**—Murine 3T3-L1 cells (ATCC, Manassas, VA; passage 3–10) were grown to confluence and differentiated to adipocytes as described (27, 28) with minor modifications. Briefly, pre-adipocytes were cultured in Dulbecco’s modified Eagle’s medium and 10% fetal bovine serum. Two days after reaching confluence, cells were differentiated by treatment with 10 μg/ml insulin, 0.5 mM methylisobutylxanthine, and 1 μM dexamethasone in Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum for 2 days. Cells were then maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum and 5 μg/ml insulin. All experiments were performed on post-differentiation day 8 to day 10. Human monocyte-derived macrophages were isolated and cultured as previously described (24).

**RNA Preparation and RT-PCR**—Cytoplasmic RNA was extracted from fully differentiated adipocytes grown on six-well plates using the RNeasy mini kit (Qiagen). RT-PCR was performed using 200 ng of RNA and the one-step Calypso RT-PCR kit from DNAmp Ltd. The apoE and β-actin primer pairs were described previously (24). Reverse transcription was carried out at 50 °C for 30 min and then terminated at 94 °C for 2 min. Amplifications were pre-terminated to be within a linear range by varying template levels and number of cycles. The PCR products were resolved on agarose gels and stained with ethidium bromide. The apoE primer pair produced a 505-bp product, and the β-actin primer pair produced a 924-bp product. The images were captured using a Bio-Rad Gel Doc-IT system (UVP, Upland, CA) and quantitated using ImageQuant. The primer pair produced a 503-bp product, and the other primer pair produced a 924-bp product. The images were captured using a Bio-Rad Gel Doc-IT system (UVP, Upland, CA) and quantitated using ImageQuant.

**Regulation of Adipocyte ApoE Expression**—Differentiated adipocytes were electroporated using the Gene Pulser Xcell (Bio-Rad) with a setting at 180 V and 940 microfarads. Briefly, the cells were trypsinized and washed three times in Dulbecco’s phosphate-buffered saline without CaCl2 and MgCl2. The cells were then suspended at 107/ml in phosphate-buffered saline, and 0.5 ml of cell suspension was transferred to a 0.4-cm gap cuvette. Twenty-five μg of apoE reporter plasmid DNA, 2.5 μg of the β-galactosidase internal control, and 200 μg of carrier DNA (sheared herring sperm DNA, Roche Applied Science) were added to electroporation buffer. The cells were then placed on ice and allowed to recover for 24 h in 10% fetal bovine serum before use in experiments. Luciferase and β-galactosidase activity was measured in cell extracts using kits available from Promega according to the manufacturer’s instructions. Firefly luciferase activities were normalized to β-galactosidase activity to calculate relative luciferase units.

**Human Subject Treatment Protocol**—Subjects signed consent forms to a protocol that was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences (UAMS) and was conducted on the UAMS General Clinical Research Center. Subjects were recruited who were in good health but with impaired glucose tolerance, with a fasting glucose under 100 mg/dl and a 2-h post-challenge glucose of 140 to 199 mg/dl following a standard oral 75-g glucose challenge. Subjects were weight-stable and were controlled on a 35% fat, eucaloric diet throughout the study. A subcutaneous fat biopsy was performed by incision from the lower abdominal wall, and adipose tissue was immediately placed into liquid nitrogen for subsequent RNA extraction, as described previously (32). Insulin sensitivity was measured using the frequently sampled intravenous glucose tolerance study using 11.4 g/m2 glucose and 0.04 units/kg insulin (33). Insulin was measured using an immunoenzymimessence assay (MLT Assay, Wales, UK), and glucose was measured in duplicate by a glucose oxidase assay. The insulin sensitivity index (SI) was calculated using the MinMod program. SI is an index of insulin sensitivity based on the dynamic relationship between circulating insulin and glucose levels after the intravenous injection of glucose and insulin, with low values indicating insulin resistance. The insulin sensitivity index derived from this test is highly correlated with the insulin sensitivity index derived from the euglyc-
mic clamp (34). Subjects were treated with pioglitazone for 10 weeks beginning at 30 mg/day for 2 weeks and then 45 mg/day for an additional 8 weeks. Compliance and laboratory tests were monitored three times during the follow-up phase, and then repeat adipose tissue biopsies and insulin sensitivity testing were performed.

RESULTS

We measured the effect of the PPARγ agonist, ciglitazone, on apoE expression in 3T3-L1 adipocytes (Figs. 1 and 2). As shown in Fig. 1, treatment with ciglitazone increased the abundance of adipocyte apoE mRNA by 2–4-fold in a dose-dependent manner. The results in Fig. 2 demonstrate that treatment of adipocytes with ciglitazone (30 μM) increased cell-associated and secreted apoE protein as detected by immunoblot. In three independent experiments there was a 2.5-fold increase in cell-associated apoE and a 3.6-fold increase in secreted apoE after treatment with ciglitazone, similar to the magnitude of increase in the apoE mRNA level. We next performed experiments to assess the specificity of the apoE gene response to ciglitazone. Insulin is an important regulator of adipocyte gene expression (35). PPARγ is poorly expressed in adipocytes; however, PPARγ agonists have been reported to modulate adipocyte gene expression (36). Neither insulin nor the PPARγ agonist, WY14643, influenced adipocyte apoE mRNA abundance (Fig. 3). As an additional evaluation of specificity, we examined the response of the apoE gene in human monocyte-derived macrophages to ciglitazone. When examining time points up to 48 h of treatment over a range of ciglitazone doses, there was no change in human monocyte-derived macrophage apoE expression (not shown).

The study of PPARγ agonist-regulated gene expression is of particular interest due to the widespread use of these agents in humans. Therefore, we next evaluated whether systemic treatment of insulin-resistant, non-diabetic subjects with the PPARγ agonist pioglitazone would influence apoE gene expression in adipose tissue. Three female subjects with impaired glucose tolerance were treated with pioglitazone for 10 weeks using the protocol described under “Experimental Procedures.” For the duration of this treatment, the subjects were placed on a weight-maintaining diet containing 35% of calories from fat. Subcutaneous abdominal adipose tissue was collected before and after treatment with pioglitazone. Results obtained from these studies are given in Table I. The glycohemoglobin was in the normal range before and after treatment with pioglitazone, as was the fasting blood glucose, although the fasting blood glucose modestly decreased after treatment in all three subjects. Improved insulin sensitivity, expected with pioglitazone treatment, was demonstrated by the increase in the insulin sensitivity index, SI, measured at 10 weeks in all three subjects. With respect to apoE gene expression, treatment of subjects with pioglitazone produced a 2–3-fold increase in apoE mRNA abundance, as measured using real time RT-PCR. The magnitude of the apoE gene response measured in adipose tissue exposed to a PPARγ agonist in vivo was similar to that produced in isolated 3T3-L1 adipocytes treated with ciglitazone.
The above results demonstrated the in vivo effect of a PPARγ/H9253 agonist on increasing systemic insulin sensitivity and adipose tissue apoE gene expression. TNFα has been implicated in reducing insulin sensitivity and is an important modulator of adipocyte gene expression in vivo and in vitro. We, therefore, next evaluated the effect of TNFα on apoE expression in 3T3-L1 adipocytes (Figs. 4 and 5). Treatment of adipocytes with 20 ng/ml TNFα led to an approximate 60% reduction in apoE mRNA abundance (Fig. 4). Furthermore, this reduction was reflected in an approximate 60% decrease in apoE protein secretion into the medium during TNFα treatment at 20 ng/ml (Fig. 5).

Although most TNFα in adipose tissue may derive from macrophages, low levels of TNFα may be expressed by adipocytes in the presence of obesity (37–40). PPARγ agonists have been shown to suppress TNFα expression in adipocytes (40). It has further been shown that suppression of most adipocyte genes by TNFα is mediated via NFκB, and PPARγ agonists can interfere with transcriptional activity of NFκB (40, 41). Therefore, the opposing effects of TNFα and ciglitazone on apoE expression in adipocytes could result from regulatory interactions that impinge on a single gene regulatory locus. We addressed this mechanism and obtained additional insight into how PPARγ agonists influence apoE expression in adipocytes by analyzing portions of the apoE gene control elements for their responsiveness to TNFα and ciglitazone. The results of the first series of experiments are shown in Fig. 6. The proximal promoter portion of the apoE gene (pGL623) has been shown to contain numerous potential regulatory elements and binding sites for transcription factors (15–19) but does not respond to the PPARγ agonist. Inclusion of a downstream con-
Control element with a high degree of homology to the consensus PPARγ response element (pGL233PPAR), which has been demonstrated to transduce an apoE gene response to ciglitazone in a human astrocytoma cell line (31), also did not respond to ciglitazone in adipocytes. However, inclusion of a distal downstream enhancer element (20) that has been previously shown to contain a functionally important LXR response element (pGL623 enhancer) demonstrated a robust response to ciglitazone. In Fig. 7 we present the results of a representative experiment examining the responsiveness of pGL623 and PGL623 enhancer constructs expressing luciferase, which was statistically significant (p < 0.02).

The addition of ciglitazone plus TNFα did not increase expression of the pGL623 construct compared with TNFα alone.

**DISCUSSION**

There has been increasing interest in adipose tissue as a metabolically active energy depot that modulates organismal energy balance by regulating substrate availability and by secreting factors that modulate substrate metabolism in distant tissues. There is also increasing interest in the effect of PPARγ agonists in the regulation of adipose tissue function. This interest is driven not only by the significant effect of these agents on adipocyte gene expression but also by the widespread use of PPARγ agonists to treat human diabetes. In this report we demonstrate a significant effect of a PPARγ agonist, ciglitazone, on apoE gene expression and on apoE secretion in adipocytes. The effect of ciglitazone on the apoE gene is transduced by a 620-bp downstream enhancer element located 3.3 kilobases downstream of the apoE gene within the apoE/apoCI intergenic region. Interestingly, this enhancer contains a conserved functional LXR response element. Because the expression of LXRα is positively regulated by PPARγ agonists in adipocytes (42–45), this LXR element, in the presence of an endogenously generated ligand, could account for increased apoE gene expression in response to ciglitazone. On the other hand, a functional PPARγ response element has also been identified for transducing the apoE gene response to ciglitazone in U87MG astrocytoma cells (31). This element is located 2 kilobases downstream of the apoE gene in the apoE3/CI intergenic region. In our experiments, however, we could not demonstrate a response to ciglitazone mediated by this PPARγ response element in adipocytes. Only the construct containing the more distal 620-bp enhancer demonstrated a response.

Our results also demonstrate that TNFα suppresses apoE gene expression in adipocytes and that TNFα and PPARγ ago-
nists regulate apoE gene response via distinct apoE gene control elements. The downstream enhancer mediates the effect of TNFα. Many of the suppressive effects of TNFα on adipocyte gene expression have been found to require NFκB, and there are multiple regions of the apoE proximal promoter with significant homology to the NFκB consensus binding site. The interplay between TNFα and PPARγ in modulating adipocyte apoE gene expression in vivo may be complex. Not only can PPARγ agonists reduce TNFα expression in adipose tissue, but systemic treatment with TNFα has been shown to reduce PPARγ expression (46).

We have also demonstrated that treatment of human subjects with a PPARγ agonist increases expression of apoE in adipose tissue. Biopsies of adipose tissue contain adipocytes as well as stromal cells and macrophages, and both macrophages and adipocytes express apoE. It has been reported that apoE gene expression in the THP-1 monocyte line is increased by ciglitazone treatment (31). We, however, did not detect increased apoE expression in primary cultures of human monocyte-derived macrophages after treatment with ciglitazone. This result is in agreement with findings in primary cultures of mouse peritoneal macrophages in which treatment with PPARγ agonists also failed to increase apoE expression (47). A potential explanation for the differential response of the macrophase versus the adipocyte apoE gene to PPARγ agonists may be in the differential response of the LXRs gene. Treatment of macrophages compared with adipocytes with PPARγ agonists may be relatively less effective in increasing LXRα expression (42–45, 48, 49). Alternatively, an endogenous ligand for LXR could be more efficiently generated in adipocytes compared with macrophages during treatment with a PPARγ agonist. It is also of interest that the effect of TNFα on apoE gene expression in adipocytes and macrophages is divergent. The current results indicate that TNFα suppresses adipocyte apoE expression. However, we have previously shown that TNFα induces apoE expression in macrophages (50). Based on our observations using human monocyte-derived macrophages along with observations using isolated adipocytes, we believe that the increased apoE expression found in adipose tissue after treatment with PPARγ agonists in humans is most likely accounted for by adipocyte apoE.

The observation that adipocytes synthesize and secrete apoE and its regulation by PPARγ agonists and TNFα raises an issue regarding the potential significance of adipocyte-derived apoE. Secretion of apoE by adipocytes could have a systemic effect. For example, increased plasma apoE level has been shown to reduce systemic markers of oxidant stress, and this effect can be demonstrated in the presence of normal background expression of apoE (13). However, a role for adipocyte-derived apoE in adipose tissue homeostasis may be more likely. ApoE is highly expressed in cell types that experience large lipid fluxes (e.g., vessel wall macrophages, steroidogenic cells) and is involved in modulating these lipid fluxes. This is particularly true for the cellular flux of free cholesterol. Adipocytes contain one of the largest stores of cholesterol in the body, mostly in the form of free cholesterol. An effect of apoE on adipocyte cholesterol flux and content could have substantial implications for the differentiated function of adipocytes. For example, it has been shown that perturbing the cholesterol content of adipocyte membranes leads to alterations in the expression and/or function of Glut-4, scavenger receptor BI, ABCA1, and caveolin-2 (51, 52). Perturbing adipocyte cholesterol content also modulates the expression of genes for secretion products including TNFα, interleukin-6, and angiotensinogen (51). Adipocyte-derived apoE could also modulate uptake of pericellular lipoproteins by adipocytes and thereby influence their differentiation. For example, very low density lipoprotein uptake by adipocytes has been reported to induce differentiation (53). This occurs, however, only in the presence of apoE. Very low density lipoprotein devoid of apoE does not influence adipocyte differentiation. Adipocytes could, therefore, provide a proximate source of apoE available to very low density lipoprotein particles present in the microvasculature of adipose tissue.

In summary, we have shown that PPARγ agonists and TNFα produce opposite changes in adipocyte apoE expression. TNFα suppresses adipocyte apoE expression via gene control elements that are distinct from those that transduce PPARγ stimulation but substantially reduces the absolute level of gene expression during PPARγ stimulation. ApoE plays an important role in the physiology of multiple cell types. Given the emerging importance of adipocytes and adipose tissue in several common metabolic disorders (obesity, diabetes, atherosclerosis), it will be important to understand the role of adipocyte-derived apoE on adipose tissue and organismal metabolism. Furthermore, it will be important to understand if disordered adipocyte apoE function plays a role in the metabolic complications that accompany obesity.

Acknowledgment—We thank Stephanie Thompson for assistance with manuscript preparation.

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J. Biol. Chem. 2004, 279:47626-47632.
doi: 10.1074/jbc.M408461200 originally published online August 31, 2004

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