Thiazolidinediones Repress \textit{ob} Gene Expression in Rodents Via Activation of Peroxisome Proliferator–activated Receptor γ

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Abstract

The \textit{ob} gene product, leptin, is a signaling factor regulating body weight and energy balance. \textit{ob} gene expression in rodents is increased in obesity and is regulated by feeding patterns and hormones, such as insulin and glucocorticoids. In humans with gross obesity, \textit{ob} mRNA levels are higher, but other modulators of human \textit{ob} expression are unknown. In view of the importance of peroxisome proliferator–activated receptor γ (PPARγ) in adipocyte differentiation, we analyzed whether \textit{ob} gene expression is subject to regulation by factors activating PPARs. Treatment of rats with the PPARγ activator fenofibrate did not change adipose tissue and body weight and had no significant effect on \textit{ob} mRNA levels. However, administration of the thiazolidinedione BRL49653, a PPARγ ligand, increased food intake and adipose tissue weight while reducing \textit{ob} mRNA levels in rats in a dose-dependent manner. The inhibitory action of the thiazolidinedione BRL49653 on \textit{ob} mRNA levels was also observed in vitro. Thiazolidinediones reduced the expression of the human \textit{ob} promoter in primary adipocytes, however, in undifferentiated 3T3-L1 preadipocytes lacking endogenous PPARγ, cotransfection of PPARγ was required to observe the decrease. In conclusion, these data suggest that PPARγ activators reduce \textit{ob} mRNA levels through an effect of PPARγ on the \textit{ob} promoter. (\textit{J. Clin. Invest.} 1996. 98: 1004–1009.) Key words: obesity • antidiabetic • adipocyte • adipose

Introduction

Obesity, a disorder of energy balance, represents a major health problem and is usually associated with complications including cardiovascular disease, diabetes, and an increased mortality rate (1). Obesity or predisposition to obesity has a strong genetic component (2). In the \textit{ob/ob} mouse, a single gene mutation results in profound obesity that is often accompanied by diabetes (3). Using positional cloning techniques, Friedman and colleagues identified the mouse \textit{ob} gene and its human homologue (4) and demonstrated that expression of the \textit{ob} gene is limited to adipose tissue. In mutant SM/Ckc-\textit{ob/ob} mice, a genomic alteration results in the complete absence of \textit{ob} mRNA, whereas in C57BL/6J-\textit{ob/ob} mice, a nonsense mutation results in a truncated, nonfunctional protein. Studies with specific antibodies confirmed the presence of the \textit{ob} gene product, leptin, in plasma of normal mice and its absence in plasma of \textit{ob/ob} mutants (5). Before the identification of the \textit{ob} gene, a role for leptin as a satiety factor was proposed based on data derived from parabiosis experiments (6). When \textit{ob/ob} mice were made parabiotic with normal mice, they curbed their eating and lost weight, suggesting that they were responsive to a blood-borne satiety factor produced by the normal partner (6). Furthermore, leptin injection reduces food intake, increases energy expenditure, induces weight loss, and normalizes metabolic parameters such as insulin and glucose in wild-type, diet-induced obese and C57BL/6J \textit{ob/ob} mice (5, 7–10).

A potential mechanism of leptin’s signaling action was elucidated recently when a leptin receptor was cloned (11, 12). This receptor is related to the gpl30 signal transducing component of the IL-6, G-CSF, and LIF cytokine receptors (11). The receptor is highly expressed in the choroid plexus and maps to a position on mouse chromosome 4 encompassing the \textit{db} locus. It is therefore tempting to speculate that leptin provides the central nervous system with a signal triggering multiple effector pathways leading to leptin’s pleiotropic effects.

To completely understand leptin’s role in energy metabolism, it is necessary to delineate the factors involved in \textit{ob} gene regulation. Recent studies have demonstrated that the expression of the \textit{ob} gene is itself controlled by the nutritional status of the animal. Fasting reduces, whereas food intake increases, \textit{ob} gene expression (13–16), an effect accounted for by changes in plasma insulin levels (14, 16). Glucocorticoids have also been shown to regulate \textit{ob} gene expression (17, 18). Furthermore, in overtly obese humans (19–23) and in several animal models of obesity, such as the \textit{db/db} mouse, Zucker \textit{fa/fa} rats, and VMH-lesioned rats (5, 13, 24–28), which do not appear to respond to leptin, \textit{ob} mRNA and circulating leptin levels are increased. These findings suggest that upregulation of \textit{ob} mRNA levels occurs as a homeostatic mechanism.

Since the \textit{ob} gene is exclusively expressed in adipocytes, we have initiated studies to examine the role of adipogenic factors in the expression and regulation of the \textit{ob} gene. The expression of two important adipocyte transcription factors, peroxisome proliferator–activated receptor γ (PPARγ) and C/EBPα, is induced during adipocyte differentiation and these factors

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Received for publication 29 February 1996 and accepted in revised form 19 June 1996.

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1. Abbreviations used in this paper: C/EBP, CAAT/enhancer binding protein; PPAR, peroxisome proliferator–activated receptor; PPRE, PPAR response element.
are maintained in the mature adipocyte. Several adipocyte-specific genes have binding sites for these factors in their promoters and have been shown to be transcriptionally responsive to chemical modulators of these factors (reviewed in reference 29). Recent studies by our group and others have characterized the role of C/EBPβ in ob gene expression, an effect mediated by a C/EBP site in the proximal ob gene promoter (30, 31). The present study was undertaken to better understand the role of PPARγ, the other key transcription factor implicated in the determination of the adipocyte phenotype, in ob gene expression. In these studies, we demonstrate that expression of the ob gene is reduced by PPARγ and its activators both in vivo and in vitro.

Methods

Reagents. BRL 49653 was synthesized at Ligand Pharmaceuticals (San Diego, CA), whereas fenofibrate was a generous gift of Dr. Alan Edgar of Fournier (Dijon, France). All other reagents were obtained from the usual sources.

Animal studies. Adult Sprague-Dawley rats were divided into groups of four animals each. They were group housed and accustomed to a 12:12 h day–night illumination cycle (light from 8 a.m. to 8 p.m.). In one series of experiments, the effects of BRL 49653 were analyzed. In the first study, rats received BRL 49653 (1, 2, or 5 mg/kg per d) or vehicle alone (1% carboxymethylcellulose) for 7 d by gavage. In a second experiment, rats were dosed with either 5 or 10 mg/kg per d. In a third study, controls were compared with animals that received 0.5% wt/wt of fenofibrate mixed with their food over 14 d. In a final study, we analyzed adipose tissue ob mRNA levels in rats fed a high-fat diet containing 20% hydrogenated coconut oil (controls) or 20% menhaden (fish) oil for 3 mo. All animals were killed by exsanguination under ether anesthesia between 8 and 10 a.m. Epidydimal adipose tissue was removed, rinsed with 0.9% NaCl, and frozen in liquid nitrogen until RNA preparation.

Cell culture. Primary rat adipocytes were obtained exactly as described by Hajduch et al. (32). Standard cell culture conditions were used to maintain 3T3-L1 cells obtained from American Type Culture Collection (Rockville, MD). BRL 49653 and fenofibrinic (in DMSO) were added to the medium at the appropriate concentrations and quantification of total cellular RNA were performed as described previously (16). To test the activity of the human ob gene promoter (30, 34). The hamster pSG5-αGal-PAR/β expression vector has been described elsewhere (35). Transfections were performed using either standard calcium phosphate precipitation techniques for 3T3-L1 preadipocytes (36) or electroporation for primary adipocytes having either standard calcium phosphate precipitation techniques for transfection efficiency. Luciferase assays were carried out exactly as described previously (37).

Results

Food intake and adipose tissue weights increase and ob mRNA levels decrease after administration of PPARγ but not PPARα activators to rats. Adipocyte differentiation has been shown to be determined by the coordinately acting transcription factors PPARγ (30, 38, 39) and various members of the C/EBP family (reviewed in reference 40). Previous studies by our group (30) and others (31) demonstrated the critical role of C/EBPβ in the expression of the ob gene. In these studies, we addressed the role of PPARγ in ob gene regulation. We first tested the effects of the antidiabetic thiazolidinedione BRL 49653, previously shown to be a high affinity ligand for PPARγ (41, 42), on the expression of the ob gene in vivo in rats. In animals receiving BRL 49653 at increasing doses (0, 1, 2, and 5 mg/kg per d) over 7 d, no change in either body or liver weight was observed (Table I). However, a dose-dependent increase in epidydimal fat pad weight was observed after BRL 49653 treatment (Table I). These observations are consistent with previously reported activities of the thiazolidinedione antidiabetic agents to induce adipocyte differentiation and increase adipose tissue mass (43–47). In this experiment, which used relatively low doses of BRL, food intake showed a tendency to decrease, although no statistical significance was obtained. To unequivocally establish that BRL 49653 had an effect on food intake we administered higher doses of BRL 49653 (5, 10, 20 mg/kg per d) to rats over 7 d and recorded food intake on a daily basis. In this experiment, administration of BRL at doses of 5, 10, or 20 mg/kg per d was associated with a significant increase in food intake (Fig. 1).

To analyze whether the effect of thiazolidinediones on adipose tissue involves changes in ob expression, we analyzed ob mRNA in epidydimal fat pads of these rats. ob mRNA levels decreased by 40% in rats treated with BRL 49653 at 5 mg/kg per d (Fig. 2). Other potential conditions resulting in activation of PPARγ, such as administration of a diet enriched in fish oils (20% wt/wt in food, 3 mo), also decreased ob mRNA expression significantly by 33% (Fig. 2). This indicates a possible role for fatty acid–derived PPAR activators in the regulation of ob gene expression. In contrast to the results obtained with thiazolidinediones and fish oils, administration of the PPARα activator, fenofibrate (0.5% wt/wt in food for 14 d), did not result in a reduction of ob mRNA levels (Fig. 2). Treatment of ani-

| Table I. Effects of Administration of Different Doses of BRL 49653 on Body Mass, Liver Weight, and Weight of the Epidydimal Fat Pad |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Body mass       | Epidydimal fat  | Liver           |
|                                | grams           | grams           | grams           |
| Control                         | 344±22          | 2.5±0.3         | 16.8±1.3        |
| BRL 49653 (1 mg/kg per d)       | 355±21          | 3.3±0.2*        | 17.9±1.3        |
| BRL 49653 (2 mg/kg per d)       | 361±18          | 3.8±0.5*        | 18.9±0.6        |
| BRL 49653 (5 mg/kg per d)       | 338±9           | 4.0±0.6*        | 17.4±1.8        |

*Statistically different from control, P < 0.05.
mals with fenofibrate did not result in a change in body or adipose tissue weight, whereas the typical increase in liver weight (from 13.8 ± 0.5 to 19.7 ± 2.5 grams) known to occur after treatment with peroxisome proliferators such as fenofibrate was observed (48). Furthermore, this increase in liver weight was associated with a sevenfold induction in liver acylCoA oxidase mRNA levels indicating that fenofibrate was active (49) (data not shown). The effect of BRL 49653 on ob mRNA expression was furthermore dose dependent, being most pronounced at a dose of 5 mg/kg per d (Fig. 3).

PPARγ activators control ob mRNA expression in cultured primary adipocytes. To determine whether the in vivo changes in ob gene expression are the result of a direct PPARγ effect on adipocyte ob gene expression, we evaluated the effects of BRL 49653 (100 μM; 24 h) and the PPARγ selective peroxisome proliferator, fenofibric acid (250 μM; 24 h), on ob mRNA expression in primary rat adipocytes. Whereas BRL 49653 reduced ob mRNA expression significantly in three independent experiments, no effect of fenofibrate on ob mRNA levels was detected (Fig. 4). These results thus suggest that the in vivo effects of the PPARγ ligand BRL 49653 are due to a direct cellular effect on adipocyte ob gene expression.

PPARγ modulates the ob promoter at the transcriptional level. We next studied the effects of coexpression of PPARγ in the presence or absence of PPAR activators on the ~3 kb human ob promoter construct pGL3-OB1 (30). In primary rat adipocytes, cotransfection of the PPARγ expression vector (pSGS-cgPPARγ) in the absence of activators had no effect (Fig. 5 A). When the thiazolidinedione, pioglitazone, was added (10 μM), a 30% decrease in ob promoter activity was observed. Combination of PPARγ plus pioglitazone led to an additional decrease to ~50% (Fig. 5 A). When a more potent thiazolidinedione, such as BRL 49653 (10 μM), was used in rat primary adipocytes, promoter activity was reduced 60% and cotransfection of PPARγ had no further effect, suggesting the
Discussion

The association of murine obesity with mutations in the ob gene has generated intense interest in molecular studies aimed at delineating factors potentially involved in human obesity. In this study, we determined whether the expression of the ob gene is under the control of PPAR\(_\gamma\), a key transcription factor involved in adipocyte-specific gene expression. PPREs have been characterized in several genes involved in the control of lipid and fatty acid metabolism (reviewed in reference 29). In addition, several key adipocyte genes have been shown to be induced by PPAR\(_\gamma\) activators and to contain functional PPREs in their regulatory sequences (e.g., lipoprotein lipase, Schoonjans, K., and J. Auwerx, unpublished observations; 36, 38, 50, 51). Furthermore, it was recently reported that antidiabetic thiazolidinediones (41, 42) and prostaglandin derivatives (42, 52) are direct and specific ligands for PPAR\(_\gamma\). The identification of prostaglandins as the endogenous PPAR\(_\gamma\) ligand and the capacity of other fatty acids to activate this transcription factor provides a mechanistic explanation of the ability of fatty acids (38, 53, 54) and arachidonic acid (55) to induce adipocyte differentiation.

Despite the fact that ob expression is associated with the differentiated adipocyte phenotype and PPAR\(_\gamma\) is a key transcription factor triggering and maintaining this phenotype, PPAR\(_\gamma\) activation does not induce ob expression. To the contrary, PPAR\(_\gamma\) ligands decrease ob expression both when administered in vivo and when added to cultured adipocytes in vitro. Furthermore, PPAR\(_\gamma\) decreases transcription of a reporter gene driven by \(~3,000\) bp of the human ob promoter. This negative effect on ob gene expression appears to be specific for compounds capable of activating PPAR\(_\gamma\), since fenofibrate, a potent PPAR\(_\alpha\) activator, has no effect on ob gene expression. PPARs heterodimerize with RXRs and these heterodimers exert their effects on transcription via interaction with a PPRE, composed of a direct repeat of the nuclear receptor hexanucleotide core recognition motif spaced by 1 nucleotide (reviewed in reference 29). We were unable to identify by homology search a consensus PPRE in the ob gene promoter. In view of the rather unusual negative effects of PPAR\(_\gamma\) by thiazolidinediones on ob gene transcription and the absence of a consensus PPRE, it will be important to identify the molecular mechanism underlying this negative regulation. This phenomenon is reminiscent of the negative effects of PPAR\(_\alpha\) modulators on apo C-III expression in the liver (49, 56). It is therefore tempting to speculate that the repressive effects of PPAR\(_\gamma\) on the human ob gene promoter might be mediated through interactions with positive modulators of ob transcription, such as C/EBP\(_\alpha\) or Sp1 (30).

The observed decrease in ob gene expression after treatment with BRL 49653 in the presence of an increase in adipose tissue mass is very interesting and suggests that body mass and ob gene expression can be regulated in opposite fashion (e.g., by pharmacological treatment with PPAR\(_\gamma\) activators). This situation is in contrast with both the overexpression of ob mRNA observed in several obese animals, such as the db/db mice, Zucker fa/fa rats, and VMH-lesioned rats (5, 13, 24–28), and with the positive correlation between body mass index and ob mRNA or plasma leptin observed in humans (19–23). The physiological importance of this discordance between ob mRNA levels and adipose tissue mass after thiazolidinedione treatment is unclear at present. It is, however, tempting to speculate that the uncoupling of adipose tissue mass and ob gene expression might be implicated in mediating the effects of thiazolidinediones on insulin resistance. In vivo, PPAR\(_\gamma\)'s activities to reduce leptin levels may lead to increased caloric uptake, thus favoring energy storage into adipocytes. In that context, the effects of PPAR\(_\gamma\) modulators on ob gene expression and other adipocyte-specific target genes, such as lipoprotein lipase (Schoonjans, K., and J. Auwerx, unpublished observations), fatty acid transporter protein (Martin, G., B. Staels, and J. Auwerx, unpublished observations), aP2 (39), and acyl-CoA synthetase (36, 51) will lead to increased energy uptake and storage in the adipocyte. The reduction in ob gene expression after PPAR\(_\gamma\) activation might therefore explain two well-known but ill-understood phenomena. First, the PPAR-mediated reduction in ob gene expression might underly the increase in adipocyte differentiation and adiposity associated with treatment with thiazolidinedione antidiabetic agents (43–47). Results from our experiments confirm the adipose tissue weight gain in animals receiving BRL 49653, showing a significant dose-dependent increase in these animals. The absence of an effect on total body weight in this study, in contrast to other studies reported in the literature.

Figure 5. ob promoter activity is regulated by PPAR\(_\gamma\). (A) Promoter activity of the pGL3-OB1 construct was analyzed in primary rat adipocytes. Luciferase activity was determined in cells transfected with either 5 \(\mu\)g of pSG5-cgPPAR\(_\gamma\) or the empty pSG5 expression vector in the presence or absence of 10 \(\mu\)M pioglitazone or 10 \(\mu\)M BRL 49653. Cells were exposed to the compounds for 24 h. *\(P < 0.05\); **\(P < 0.01\). (B) Promoter activity of the pGL3-OB1 (2 \(\mu\)g) construct was analyzed in 3T3-L1 preadipocytes. Luciferase activity was determined in cells cotransfected with either 2 \(\mu\)g of pSG5-cgPPAR\(_\gamma\) or the empty pSG5 expression vector in the presence or absence of 10 \(\mu\)M BRL 49653. Cells were exposed to BRL 49653 for 24 h. The mean of four points is shown. Experiments were performed at least three times. *\(P < 0.05\).
(57–59), is most likely due to the short time BRL 49653 was administered in our experiments. Second, it is tempting to speculate that the increase in fatty acids delivered to the adipocyte by a high-fat meal could be involved in stimulating adipose PPARγ activity. The ensuing decrease in ob gene expression and leptin levels would be associated with a smaller suppression of appetite. In fact, clinical data have shown that high fat meals are known to be less satiating than equicaloric carbohydrate-rich meals (60, 61).

In conclusion, we have demonstrated that ob gene expression is reduced both in vivo and in vitro by PPARγ activators. These compounds have a direct effect on the ob promoter. Knowledge of sequence elements involved in this regulation and identification of factors such as PPARγ regulating ob gene expression should be of major importance in our understanding of adipocyte physiology and obesity.

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