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Bezafibrate improves bacterial lipopolysaccharide-induced dyslipidemia and anorexia in rats

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Abstract

Bacterial endotoxin/lipopolysaccharide (LPS)-induced cachexia is characterized by weight loss, anorexia, and a disturbance in lipid metabolism, namely, hypertriacylglycerolemia. The aim of this study in rats with acute endotoxicity induced by an injection of LPS was to investigate whether bezafibrate, a ligand for peroxisome proliferator–activated receptor α and a lipoprotein lipase (LPL) activator, improved cachectic conditions, including impaired lipid metabolism. Short-term administration of LPS in the rats resulted in impairment of triacylglycerol clearance in plasma after the intake of fresh cream. In addition, LPS increased whole-body energy expenditure, reduced fasting body weight and caused anorexia in the rats. Bezafibrate treatment resulted in significant improvements in LPS-induced dyslipidemia and anorexia, but had no effect on energy expenditure, respiratory quotient, or fasting body weight in the endotoxic rats. Administration of LPS was also associated with a decrease in the level of messenger RNA (mRNA) expression for LPL in white adipose tissue and skeletal muscle and an increase in the mRNA levels for uncoupling protein 3 in skeletal muscle. Bezafibrate treatment reversed the decline in LPL mRNA levels in white adipose tissue but not in the skeletal muscle tissue of the rats. The enhanced uncoupling protein 3 mRNA level in the endotoxic rats was not affected by bezafibrate treatment. Plasma concentration of leptin was increased by short-term LPS treatment. Bezafibrate decreased the level of plasma leptin significantly without affecting the level of leptin mRNA expression. These results suggest that bezafibrate may be an effective drug not only for impaired triacylglycerol metabolism, but also for anorexia in cachectic states induced by bacterial infections.

1. Introduction

Many chronic or end-stage diseases, such as infections, cancer, AIDS and congestive heart failure, are associated with cachexia [1]. Both cancer-induced and bacterial endotoxin/lipopolysaccharide (LPS)-induced cachexia have been investigated extensively and are characterized by weight loss, anorexia, and the breakdown of body fat and skeletal muscle protein [1-3]. Hypertriacylglycerolemia is also a major hallmark of these types of cachectic syndromes [4-6]. For instance, bacterial sepsis in humans and injection of LPS into animals result in disturbances in lipid metabolism, mainly as a consequence of delayed clearance of triacylglycerol-rich lipoproteins from the circulation [5]. Cancer-type cachexia is also associated with hypertriacylglycerolemia [4], with this impaired utilization of circulating lipids leading to an accelerated reduction in body mass. Administration of LPS and the presence of infections have been demonstrated to decrease the activity of lipoprotein lipase (LPL), a key enzyme in triacylglycerol catabolism, in several tissues including heart, skeletal muscle, and adipose tissues [7,8]. This reduction in LPL activity is now considered to be the primary mechanism for the disturbance in lipid utilization induced by infection and sepsis [5].

Establishing a strategy for improving cachexia is a major goal for increasing the survival rate of patients with chronic and end-stage diseases, with several studies having focused on pharmacologic and nutritional therapies for the cachectic syndrome [1]. Recently, Hataya et al [9] reported that treatment of LPS-injected rats with ghrelin, an appetite-stimulating hormone, resulted in a slight increase in food intake and a gain in whole body weight. Furthermore,

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Kawamura et al [10] demonstrated that the LPL activators, bezafibrate and NO-1886, improved the clearance defect of circulating triacylglycerol in B16 melanoma–induced cachectic mice. Because endotoxic cachexia is associated with decreased tissue LPL activity [5,7,8], it is possible that these LPL activators may also reverse the impairment in lipid metabolism that develops in this type of cachexia. However, little is known regarding the effect of these drugs on the LPS-induced cachectic syndrome.

In the present study, we investigated whether bezafibrate, also known as a ligand for peroxisome proliferator–activated receptor α (PPAR-α) [11,12], improved disturbances in lipid metabolism in LPS-injected rats with acute endotoxicity.

2. Materials and methods

2.1. Materials

LPS (*Escherichia coli* strain 0127:B8) was purchased from Sigma (St Louis, MO) and was diluted in 0.9% saline. Bezafibrate was kindly provided by Kissei Pharmaceutical (Nagano, Japan).

2.2. Experimental protocol

Male Wistar rats, aged 8 weeks, were purchased from Japan SLC (Shizuoka, Japan). The rats were housed singly at a constant room temperature of 23°C ± 1°C with a 12-hour light/dark cycle. Food (standard nonpurified diet, Oriental Yeast, Tokyo, Japan) and water were available ad libitum until the start of the experiments.

At 9 weeks of age, the rats were fasted for 24 hours, followed by collection of blood samples from a tail vein for measurement of basal plasma glucose, lipids, and leptin levels. The rats were then assigned randomly to 3 different groups, 2 of which received an intraperitoneal injection of LPS (0.5 mg/kg body weight). The remaining group received an injection of saline alone and served as controls. After 6 hours, animals in one of the LPS-injected groups received an oral administration of bezafibrate (100 mg/kg body weight) diluted in 5% gum arabic solution. The other 2 groups received the same amount of gum arabic solution only. Because LPS is known to induce anorexia [3], the fasting state was continued for a further 18 hours before the start of the experiments described below.

2.3. Oral fat tolerance test

The procedure of the oral fat tolerance test (OFTT) has been described previously [13]. Twenty-four hours after injection of LPS (18 hours after administration of bezafibrate or gum arabic solution), fresh cream (Meiji Milk Products, Tokyo, Japan) containing 69.5% saturated fatty acids was administered orally at a dose of 4 mL/kg body weight. Blood samples were collected from a tail vein at 0, 2, 4, 6, and 8 hours after the meal for measurement of plasma glucose, triacylglycerol, and leptin levels.

2.4. Respiratory gas analysis

Energy expenditure and the respiratory quotient (RQ) for each rat were assessed by using computer-controlled, open-circuit, indirect calorimetry (Oxymax, Columbus Instruments, Columbus, OH). Before the intraperitoneal injection of LPS, the rats were placed individually in metabolic cages and respiratory gas was analyzed at 5-minute intervals over a 30-minute period for measurement of basal values. Twenty-four hours after injection of LPS (18 hours after administration of bezafibrate or gum arabic solution), expired gas was reanalyzed at 5-minute intervals for 30 minutes. The rats were then administered fresh cream immediately as described above with this intervention being conducted within 1 minute. Analysis of respiratory gas at 5-minute intervals was continued for a further 8-hour period, with expired gas being aspirated at a rate of 2.0 L/min throughout the experiment. Data were expressed as the mean of each 30-minute period.

2.5. Measurement of the amount of food intake

Twenty-four hours after the injection of LPS (18 hours after administration of bezafibrate or gum arabic solution), some of the rats were allowed free access to laboratory powdered chow and the amount of food intake was monitored.

2.6. Anatomy

Twenty-four hours after the injection of LPS (18 hours after administration of bezafibrate or gum arabic solution), some of the rats were anesthetized by an intraperitoneal injection of pentobarbital, and the gastrocnemius muscle and epididymal fat tissues were collected by surgery. The tissues were then weighed and stored at −80°C for subsequent measurement of plasma and tissue protein concentration measured with a bicinchoninic acid protein assay kit (Pierce; Rockford, IL).

2.7. Blood chemicals and leptin

The plasma level of glucose was determined by the glucose oxidase method (Toecho Super, Kyoto Daiichi Kagaku, Kyoto, Japan) and the plasma concentrations of triacylglycerol and leptin were measured by using commercial kits (triacylglycerol: Wako, Tokyo, Japan; leptin: Morinaga, Kanagawa, Japan).

2.8. Northern blot analysis

Total RNA was extracted from gastrocnemius muscle and epididymal fat tissue by use of TRIzol reagent (Invitrogen, Carlsbad, CA). A 20-μg aliquot of total RNA was subjected to electrophoresis on a 1% denaturing agarose gel and then transferred to a GeneScreen membrane (NEN Life Science Products, Boston, MA). For construction of the probes, complementary DNA fragments encoding for LPL, uncou-

pling protein 3 (UCP3), and leptin were amplified by polymerase chain reaction after reverse transcription of gastrocnemius muscle or epididymal fat messenger RNA (mRNA) by a THERMOSCRIPT RT-PCR system (Invitrogen). The amplified complementary DNA fragments were cloned into the pCR 2.1-TOPO DNA vector using the TOPO TA cloning system (Invitrogen). *Eco*RI-digested fragments were then labeled with [α-^{32}P] deoxycitidine triphosphate ([α-^{32}P]dCTP) by use of a Megaprime labeling system (Amersham Pharmacia Biotech, Aylesbury, UK) and used as probes. The membrane was hybridized with the probe at 42°C overnight, followed by washing and exposure to Kodak BIOMAX MS film (Kodak, Tokyo, Japan) at −80°C.

2.9. Statistical analysis

Data were expressed as mean ± SD. Data were analyzed by analysis of variance plus Bonferroni multiple comparison tests, with $P < .05$ being considered statistically significant.

3. Results

3.1. Body weight, tissue weight, and protein concentration in muscle and plasma

The percentage decline in body weight during the 24-hour fast was significantly higher in LPS-injected rats than in saline-injected control rats (Fig. 1A). Bezafibrate administration did not affect the change in body weight induced by LPS (Fig. 1A). No significant difference was observed in the volume of water intake in the 3 groups during the experiments (data not shown). Fig. 1B shows the amount of gastrocnemius muscle and epididymal fat collected and the protein concentrations in the muscle and plasma samples. No differences in any of these parameters were observed among the 3 groups.

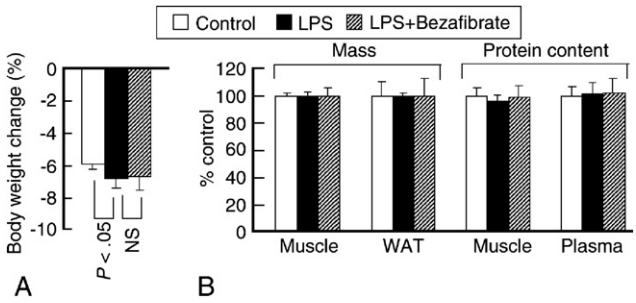

Fig. 1. A, Body weight changes after LPS and bezafibrate administration. The rats were fasted for 24 hours, weighed (basal body weight) and then divided into 3 groups. Two groups (LPS and LPS + bezafibrate) received an intraperitoneal injection of LPS (0.5 mg/kg body weight). One group received an injection of saline alone and served as controls. After 6 hours, one of the LPS-injected groups received an oral administration of bezafibrate (100 mg/kg body weight). The other 2 groups received the same amount of vehicle only. After a further 18 hours of fasting, the body weight of each rat was measured. Data are expressed as percent changes from basal body weight. NS indicates not significant. B, The amount (mass) of gastrocnemius muscle, epididymal fat (white adipose tissue [WAT]), and concentration of total protein in gastrocnemius muscle and plasma after LPS and bezafibrate administration. The mean values of the control group were designated as 100%. Data are expressed as the means ± SD of 5 rats in each group.

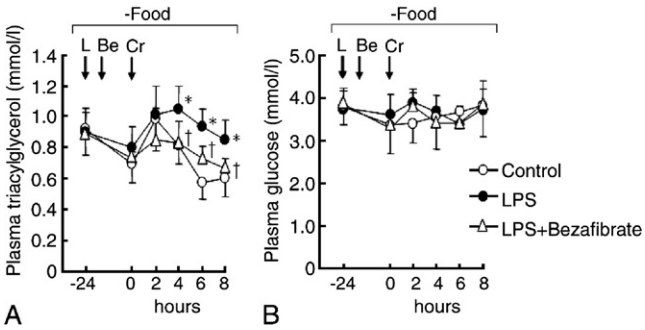

Fig. 2. Plasma triacylglycerol (A) and glucose (B) levels before (−24 hours) and during the OFTT. After LPS (L) and bezafibrate (Be) administration, fresh cream (Cr) was administered orally. Blood samples were then collected from a tail vein at 0, 2, 4, 6, and 8 hours after administration of cream. Data are expressed as means ± SD of 5 rats in each group. *$P < .05$ vs control group; †$P < .05$ vs LPS group.

3.2. Plasma levels of triacylglycerol and glucose during the OFTT

As shown in Fig. 2, administration of LPS to the rats did not affect the fasting plasma levels of triacylglycerol and glucose. However, the clearance of plasma triacylglycerol after oral administration of fresh cream was impaired in the LPS-injected rats compared with control rats (Fig. 2A). Bezafibrate treatment reversed the LPS-induced dyslipidemia (Fig. 2A). Plasma glucose levels during the oral lipid

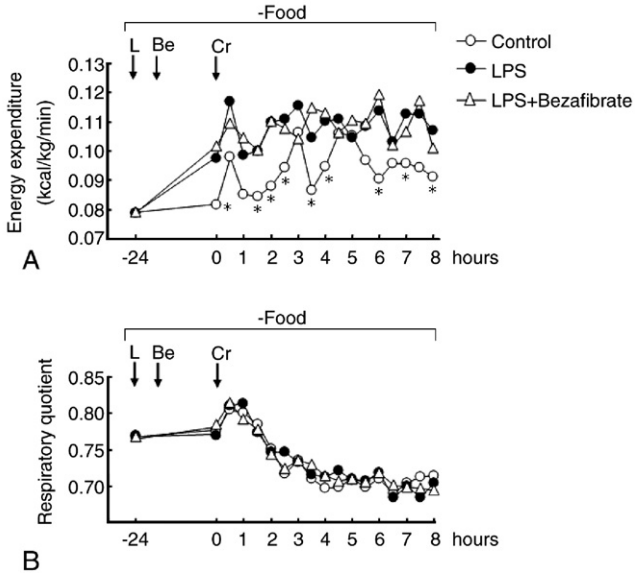

Fig. 3. Whole-body energy expenditure (A) and RQ (B) before (−24 hours) and during the OFTT. After LPS (L) and bezafibrate (Be) administration, fresh cream (Cr) was administered orally. The data are expressed as the mean of each 30-minute period for 5 rats in each group. The standard deviations are not shown to avoid overlapping with the lines. *$P < .05$ vs LPS group.

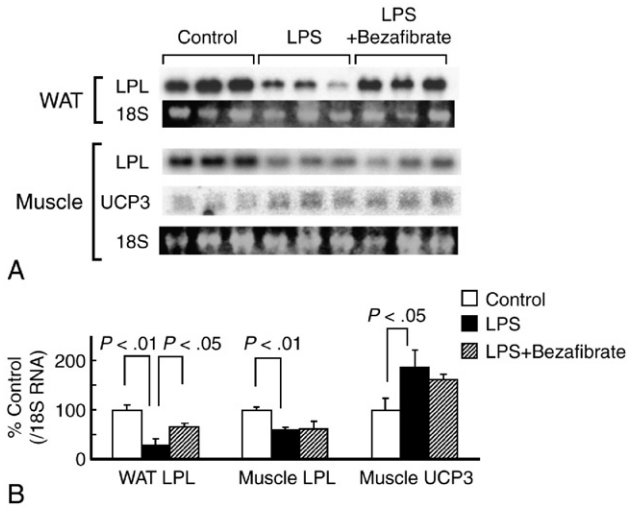

Fig. 4. A, Northern blot analysis of LPL and UCP3 in epididymal fat (WAT) and gastrocnemius muscle tissues (Muscle) for each group. The panels of 18S represent the ethidium bromide–stained 18S ribosomal RNA in the blot. B, Expression levels of LPL and UCP3 mRNA in each group determined from the density of the blotted bands in (A). Data are expressed as means ± SD of 3 rats in each group. The mean values for the control group are designated as 100%.

tolerance test were not affected by administration of LPS and/or bezafibrate (Fig. 2B).

3.3. Energy expenditure and RQ

Fig. 3 shows the results of indirect calorimetry. As shown in Fig. 3A, intraperitoneal injection of LPS caused a large increase in whole-body energy expenditure, which was sustained throughout the OFTT. Administration of bezafibrate had no effect on this LPS-induced increase in energy consumption (Fig. 3A). The RQ values during fasting and the OFTT were similar in the 3 groups (Fig. 3B).

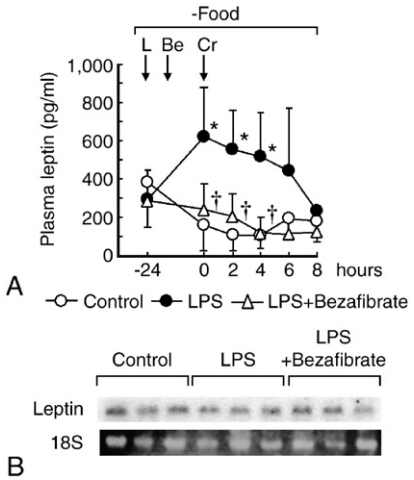

Fig. 5. A, Plasma leptin levels before (−24 hours) and during the OFTT. After LPS (L) and bezafibrate (Be) administration, fresh cream (Cr) was administered orally. Blood samples were then collected from a tail vein at 0, 2, 4, 6, and 8 hours after administration of cream. B, Northern blot analysis of leptin in epididymal fat tissues for each group (n = 3). The bottom panel represents the ethidium bromide–stained 18S ribosomal RNA in the blot. The data in (A) are expressed as means ± SD of 5 rats in each group. *$P < .05$ vs control group; †$P < .05$ vs LPS group.

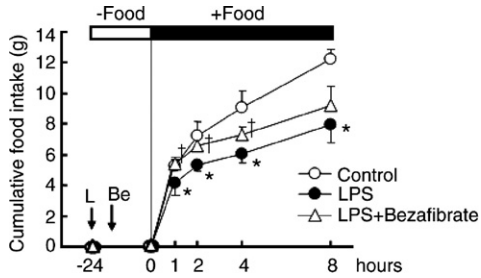

Fig. 6. The amount of food intake for each group of rats. After LPS (L) and bezafibrate (Be) administration, the fasted rats were allowed free access to powdered laboratory chow. The amount of food intake was then monitored. Data are expressed as means ± SD of 5 rats in each group. *$P < .05$ vs control group; †$P < .05$ vs LPS group.

3.4. Expression levels of LPL and UCP3 mRNA in adipose and muscle tissues

As shown in Fig. 4, Northern blot analysis revealed that the levels of LPL mRNA expression in both epididymal fat and gastrocnemius muscle tissue were decreased significantly by LPS administration. Bezafibrate treatment caused a significant reversal of the LPS-induced decline in LPL expression levels in epididymal fat, but not in gastrocnemius muscle tissue (Fig. 4). Administration of LPS increased the expression levels of UCP3 approximately 2-fold in muscle tissue, whereas bezafibrate treatment had no effect on expression levels.

3.5. Plasma concentration and tissue expression of leptin

The injection of LPS into rats resulted in marked increases in plasma leptin concentration, with these high levels persisting throughout the OFTT (Fig. 5A). This increase in plasma leptin concentration was almost completely blocked by bezafibrate treatment (Fig. 5A). The expression of leptin mRNA in white adipose tissue was not affected by administration of LPS and/or bezafibrate (Fig. 5B).

3.6. Food intake

As shown in Fig. 6, LPS administration led to a significant reduction in the amount of food intake after fasting. Bezafibrate treatment caused a partial but significant improvement in this reduction in food consumption induced by LPS (Fig. 6).

4. Discussion

The results of this study showed that short-term administration of LPS in rats resulted in impaired triacylglycerol clearance in plasma after intake of fresh cream. In addition, LPS increased whole-body energy expenditure and caused anorexia in the animals. These observations were consistent with the typical features of LPS-induced cachex-

ia, namely, the development of malnutrition and wasting conditions [3,5]. Bezafibrate treatment counteracted several of the cachectic effects of LPS and resulted in improvements in dyslipidemia and anorexia in the rats.

The precise mechanisms underlying LPS-induced hypertriacylglycerolemia remain unclear. However, several reports have suggested that LPS-induced hypertriacylglycerolemia could be attributed to increased hepatic production of very low-density lipoprotein and decreased metabolism in peripheral tissues [14,15]. In this regard, an LPS-mediated decrease in the activity of LPL in both muscle and adipose tissues is considered to be the primary reason for the impaired disposal of triacylglycerol from the circulation [5,7,8]. Evidence of this effect was reported by Gouni et al [16], who showed that administration of LPS to rats suppressed LPL activity within 7 hours in adipose and heart tissue at a posttranscriptional level. Their study, however, did not observe a concurrent decrease in LPL mRNA levels [16]. On the other hand, Hill et al [17] reported that LPS decreased LPL mRNA levels in mouse macrophages within 24 hours. They also demonstrated that LPS treatment of the macrophages altered the levels of nuclear proteins recognizing and binding the LPL promoter DNA [17]. In the present study, the expression levels of LPL in muscle and white adipose tissues decreased significantly after short-term administration of LPS (24 hours) to the rats. This indicated that in our experimental animal model, LPS-induced hypertriacylglycerolemia may be attributable, at least in part, to decreased expression levels of tissue LPL mRNA. In our study, treatment of the endotoxic rats with bezafibrate improved LPS-induced dyslipidemia significantly, with a concomitant increase in LPL mRNA levels in white adipose tissues but not in muscle tissues. Bezafibrate is a lipid-lowering drug that acts as a ligand for the PPAR-α [11,12] and has been shown to enhance the mass and activity of LPL in patients with hypertriacylglycerolemia [18]. In addition, there is evidence that bezafibrate treatment increased mRNA levels of LPL in both liver and white adipose tissue of mice [19]. However, this in vivo effect of bezafibrate was observed after a relatively long period (10 days) of the drug treatment [19]. Thus, our observations of short-term changes of LPL mRNA levels induced by LPS or bezafibrate treatment might be the consequences of the changes of mRNA turnover instead of mRNA production. The underlying mechanisms for the regulation of LPL mRNA expression levels in LPS- and/or bezafibrate-treated white adipose and muscle tissues were not determined in this study. However, our results indicate that bezafibrate improves LPS-mediated dyslipidemia and reverses the reduction in LPL mRNA expression levels in white adipose tissues.

Our data also showed that short-term administration of LPS accelerated the reduction in body weight during a 24-hour fast. Indirect calorimetry analysis revealed that LPS enhanced whole-body energy expenditure without changing the RQ. Enhanced expression of uncoupling proteins in muscle tissues is a possible mechanism to account for this increased energy expenditure caused by LPS [20]. Overexpression of UCP3 in muscle has been demonstrated to increase lipid metabolism and marginally increase oxygen consumption in mice [21]. In this regard, mice with cancer-induced cachexia and body weight reduction have been reported to have high levels of uncoupling proteins in both brown adipose and skeletal muscle tissues [22]. In accordance with this finding, our experiments showed that administration of LPS to rats actually increased UCP3 expression levels in skeletal muscle. In these endotoxic rats, bezafibrate treatment did not decrease the rate of body weight reduction, energy expenditure, or levels of UCP3 mRNA expression in skeletal muscle tissues. Son et al [23] reported that Wy-14643, another type of PPAR-α agonist, also did not affect expression levels of UCP3 in rat L6 myotubes. On the basis of these results, we concluded that bezafibrate improved LPS-induced hypertriacylglycerolemia without affecting energy expenditure and mitochondrial uncoupling in muscle tissue.

It has been reported that administration of LPS decreased LPL activity in rat heart cell cultures by inducing the production of tumor necrosis factors (TNFs) [24]. Indeed, TNF-α alone has been shown to induce cachexia and accelerate protein wasting in rats [3]. An earlier finding that Wy-14643 inhibited LPS-induced production of TNF-α [25] prompted us to examine the effect of LPS and bezafibrate on plasma cytokine levels. However, our preliminary plasma cytokine analyses revealed no increase in the plasma level of inflammatory cytokines, including interleukins and TNF-α, the day after administration of either LPS or bezafibrate (data not shown). This might indicate that neither interleukins nor TNF-α was involved in either LPS- or bezafibrate-mediated alterations in triacylglycerol metabolism. However, it is possible that the increase in levels of plasma inflammatory cytokines may occur at an earlier phase after administration of LPS. However, we did not determine the time course of changes in these inflammatory cytokine levels after LPS administration in this study.

In the present study, we observed that the injection of LPS into rats resulted in marked increases in plasma leptin concentration, and this increase was almost completely blocked by bezafibrate treatment. These observations are supported by previous studies that reported LPS increased plasma leptin levels in rodents [26,27], leading to a proposal by Francis et al [27] that leptin could be a possible mediator of LPS-induced anorexia. In our study we found administration of LPS to the rats caused a significant decrease in food intake, whereas treatment with bezafibrate led to a small but significant improvement in LPS-induced anorexia. This latter observation was in agreement with the finding of Vazquez et al [11] that bezafibrate stimulates food intake in rats. Taken together, these findings indicate that reduced production of leptin may be a contributing factor to the bezafibrate-induced inhibition of anorexia in endotoxic rats. Although it has been shown that production of leptin

correlates with the amount of adipose tissue [28], in our study we found bezafibrate attenuated the increase in plasma leptin without altering the amount of white adipose tissue. In addition, we observed that the mRNA levels of leptin in white adipose tissue were not affected by either LPS or bezafibrate treatment. The regulation of circulating leptin levels appears to be complex, involving several stages including gene expression and secretion [26-29]. Future work is therefore needed to clarify the precise mechanisms underlying the regulation of leptin levels in both endotoxic conditions and after bezafibrate treatment.

In summary, cachectic conditions develop with many chronic or end-stage diseases, such as infections, cancer, AIDS, and congestive heart failure and correlate strongly with a reduction in the survival rate of these patients. The present study indicated that bezafibrate may be an effective drug for treating impaired triacylglycerol metabolism as well as anorexia, as both conditions may be induced by bacterial infections and sepsis.

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