

Elevation of tumor necrosis factor- α induces the overproduction of postprandial intestinal apolipoprotein B48-containing very low-density lipoprotein particles: evidence for related gene expression of inflammatory, insulin and lipoprotein signaling in enterocytes

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Abstract

The aim of this study was to determine whether systemic elevation of tumor necrosis factor (TNF)- α induces intestinal-derived apolipoprotein B (apoB)48-containing very low-density lipoprotein (VLDL) production in hamsters after fat loading and whether TNF- α disturbs the related mRNA expression in inflammatory, insulin and lipoprotein signaling pathways in primary enterocytes. *In vivo* TNF- α and Triton-WR1339 infusion, Western blotting and reverse transcriptase-polymerase chain reaction were combined to explore the mechanisms underlying intestinal overproduction of apoB48-containing chylomicrons and VLDL₁ particles by TNF- α . TNF- α infusion increased intestinal production of chylomicron and VLDL₁-apoB48 in postprandial (fat load) states. Following TNF- α -treatment in enterocytes, there was enhanced gene expression of *Il1 α* and *β* , *Il6* and *Tnf* and decreased mRNA levels of components of the insulin signaling pathway including the insulin receptor (*Ir*), *Ir* substrate-1 and 2, *PI3 k*, and *Akt*, but increased phosphatase and tensin homolog deleted on chromosome ten (*Pten*) protein and mRNA expression. TNF- α also induced *Cd36* and peroxisome proliferators-activated receptor (*Ppar*) γ expression, as well as microsomal triglyceride transfer protein (*Mtp*) protein and mRNA, but suppressed the sterol regulatory element binding protein (*Srebp*)1c protein and mRNA level. Systemic elevation of TNF- α stimulates the postprandial overproduction of apoB48-containing chylomicrons and VLDL₁ particles by disturbing intestinal gene expression of the inflammatory, insulin and lipoprotein pathways. These findings provide mechanistic links among the inflammatory factor, TNF- α , intestinal inflammatory/insulin insensitivity and the overproduction of intestinal apoB48-containing lipoproteins.

Keywords: TNF- α , chylomicrons and VLDL₁-apoB48, intestinal gene expression

Experimental Biology and Medicine 2010; **235**: 199–205. DOI: 10.1258/ebm.2009.009169

Introduction

Obesity, atherosclerosis, insulin resistance and type 2 diabetes are characterized by chronic low-grade inflammation. In abdominal obesity, high visceral adipose tissue is metabolically active and secretes many inflammatory cytokines such as tumor necrosis factor (TNF)- α . Previous studies have demonstrated association between circulating TNF- α , obesity and type 2 diabetes,^{1,2} whereas others have not.³ Obesity is also associated with increased plasma TNF- α

concentrations, which fall with weight loss.⁴ Studies suggested that TNF- α profoundly affects hepatic lipid metabolism, increasing *de novo* fatty acid synthesis with a time course consistent with its ability to raise plasma triglyceride level.^{5,6} We recently reported that TNF- α infusion stimulates the overproduction of intestinal apolipoprotein B (apoB)48-containing lipoproteins⁷ and hepatic apoB100-containing very low-density lipoprotein (VLDL) particles.⁸

Growing evidence suggests that the small intestine is not merely an absorptive organ but also plays an energetic role in lipid homeostasis.^{9,10} It secretes VLDLs and chylomicrons to transport fat and fat-soluble vitamins into the blood. Studies^{10,11} confirm that both fasting and postprandial intestinal apoB48 are significantly elevated during conditions of obesity and insulin resistance. The accumulation of apoB48-containing particles in the insulin-resistant state may be an important contributor to the elevation of circulating triglyceride-rich lipoproteins (TRL)s,^{10,12} which are particularly atherogenic.¹³ In addition, recent evidence^{14,15} suggests that, postprandially apoB48-containing particles not only enhance the production of hepatic lipoproteins through increased substrate delivery in the form of chylomicron remnants, but also delay the clearance of hepatic-TRLs. Postprandially intestinal and hepatic TRLs may compete for a common, saturable metabolic pathway.^{14,15} However, little information is known about the effects of TNF- α on intestinal-derived apoB48-containing VLDL particles.

Many animal model and human population studies indicate that inflammation, insulin resistance and dyslipidemia are intimately interlinked.¹⁶ TNF- α affects insulin signaling in insulin sensitive tissues such as the liver, muscle, adipose.^{17–19} We also found that TNF- α inhibits intestinal insulin receptor (Ir)- β and Ir substrate-1 tyrosine phosphorylation as well as disturbs the phosphorylation of p38 MAPK, ERK1/2 and JNK.⁷ Here we investigated whether TNF- α induces the mRNA expression of inflammatory factors and affected the gene expression of insulin signaling pathway in small intestinal enterocytes. In addition, it is not clear whether TNF- α affects the expression of Cd36, which is important for chylomicron production and acute fatty acid uptake in the proximal intestine,¹⁶ as well as peroxisome proliferators-activated receptor (Ppar) γ , a lipid sensor that regulates lipid metabolism.²⁰

The aim of this study was to investigate whether systemic TNF- α infusion induces intestinal-derived apoB48-VLDL overproduction, using the Syrian Golden hamster model, in which lipid metabolism closely resembles that of humans.²¹ In small intestine enterocytes, we explored the effects of TNF- α on expression of genes involved in inflammatory, insulin and lipoprotein signaling pathways, which are all important underlying factors in apoB48-containing lipoproteins in the insulin-resistant state. The effects of TNF- α on the intestinal enterocyte mRNA expression of key proteins involved in intestinal lipoprotein assembly, including the microsomal triglyceride transfer protein (Mtp), and an important regulator of lipogenesis, the sterol regulatory element binding protein (Srebp)1c were measured. We present evidence that TNF- α stimulates the postprandial overproduction of apoB48-containing VLDL₁ particles, which are related to altered mRNA expression of inflammatory, insulin and lipoprotein signaling pathways.

Materials and methods

Experimental animals

Male Syrian Golden hamsters were housed individually and given free access to chow-diet and water. After a one-week

acclimatization period, the animals either underwent the *in vivo* protocol or were sacrificed for isolation of enterocytes for the *ex vivo* protocols described below.

Immunoprecipitation and immunoblotting

Enterocytes were lysed and the immunoprecipitation/immunoblotting protocols were performed as described.^{7,8,22}

In vivo TNF- α infusion and preparation of VLDL-apoB48 and chylomicron fractions

In vivo TNF- α infusion was performed essentially as described with some modifications.^{7,22} In brief, the right jugular vein of animal was exposed under ketamine anesthesia and hamsters were inserted with catheters that were exteriorized at the back of the neck and encased in silastic tubing. Five days later and after a 16-h overnight fast, each hamster was submitted to a four-hour infusion of 0.9% normal saline or TNF- α (0.5 μ g/kg/h) by the intravenous catheter. After the first two hours infusion, an intravenous bolus of Triton-WR1339 (0.5 g/kg) was administered. Triton WR-1339 effectively blocks the activity of lipoprotein lipase *in vivo* and therefore blocks the VLDL particle clearance. The secretion rate of VLDL-apoB is proportional to the rate of increase in VLDL-apoB over time.²³ After Triton-WR1339 administration, 500 μ L of blood was collected for baseline measurements. Hamsters were manually administered a 400 μ L olive oil load via oral gavage and, following a two-hour fat loading, blood samples were collected.

To isolate chylomicron and VLDL fractions, serum samples were fractionated by rate flotation ultracentrifugation. Serum sample (100 μ L) was mixed with 4 mL of 1.10 g/mL NaBr solution and loaded at the bottom of a Beckman SW41 centrifuge tube. The sample was overlaid carefully with 3 mL each of 1.065, 1.02 g/mL, and 2 mL of 1.006 g/mL NaBr solutions. After ultracentrifugation at 151,000g at 4 °C for 70 min, the top layer (1 mL), representing chylomicrons (Svedberg flotation unit [Sf], >400) was isolated and collected; and 1 mL of 1.006 g/mL NaBr solution refilled, and centrifuged under the same conditions for 18 h. The top 2 mL layer, containing VLDL particles (the top 1 mL layer for VLDL₁ [Sf, 60–400] and second layer for VLDL₂ [Sf, 20–60]), was immunoprecipitated using antiserum against hamster apoB. Measurements of chylomicrons and VLDL were performed as previously described.⁸

mRNA expression by quantitative reverse transcriptase-polymerase chain reaction

The primary enterocytes were isolated from overnight fasted hamsters anesthetized with ketamine and cultured as described.⁷ Enterocytes were treated with TNF- α (10 ng/mL) at 37 °C for 0, 0.5, 2 and 4 h. Total cellular RNA was extracted from enterocytes with Trizol[®] reagent (Invitrogen, Carlsbad, CA, USA). RNA concentrations and integrity were determined using RNA 6000 Nano Assay Kit (Agilent, Santa Clara, CA, USA). The primers used for polymerase chain reaction (PCR) are described in Table 1.

Table 1 Primers used to perform real-time PCR

Gene	Sequence (5' to 3') forward	Sequence (5' to 3') reverse
Tnf	GCTGTCGCTACATCACTGAACCT	TGACCCGTAGGGCAATTACA
Il1 α	AGGGCAGAGAGGGAGTCAACT	GGAACTTTGGCCATCTTGATTT
Il1 β	GGTTGAATCTATACCTGTCTGTGTG	TTTTCATCTTCTTCTTTGGGTATT
Il6	ACACATGTTCTCTGGGAAATCGT	AAGTGCATCATCGTTGTTTCATACA
Ir	CAAAAGCACAATCAGAGTGAGTATGAC	ACCACGTTGTGCAGGTAATCC
Irs1	GCCTGGAGTATTATGAGAACGAGAA	GGGGATCGAGCGTTTGG
Irs2	AAGATAGCGGGTACATGCGAAT	GCAGCTTAGGGTCTGGGTTCT
Pl3krl	CCTCTCCTTATAAAGCTCCTGGAA	GATCACAATCAAGAAGCTGTCGTAA
Akt	TGGACTACTTGCCTCCGAGAA	TTATCTTGATATGCCGTCCTT
Pten	AAGATGCTCAAAAAGGACAAAATGT	GATTTCTGATCACAAGACTTCCAT
Cd36	AGGAATTTGTCTATTGGGAAAGTT	CCGCAGTACCCGAGACTTCT
Ppar γ	CITGGCCATATITATAGCTGTCAATTAT	CCTCGATGGGCTTCACGTT
Mtp	GTCAGGAAGCTGTGTCAGAAATG	CTCCTTTTTCTCTGGCTTTTCA
Srebp1c	GCGGACGCACTCTGGG	ATGAGCTGGAGCATGTCTTCAAA
18S	TAAGTCCCTGCCC TTTGTACACA	GATCCGAGGGCCTCACTAAAC

Akt, thymoma viral proto-oncogene; Cd36, cluster of differentiation 36; Il, interleukin; Ir, insulin receptor; Irs, Ir substrate; Mtp, microsomal triglyceride transfer protein; P13k rl, phosphatidylinositol 3-kinase, regulatory subunit 1, Ppar, peroxisome proliferator-activated receptor; Pten, phosphatase and tensin homolog deleted on chromosome ten; Srebp, sterol regulatory element binding protein; Tnf tumor necrosis factor

The mRNA expression was determined with reverse transcriptase-PCR analysis using SYBR Green PCR Master Mix (ABI, Foster, CA, USA). The mRNA levels were normalized using the 18s rRNA levels in each sample.

Other laboratory methods

Measurements of blood glucose, insulin, triglyceride (TG) and cholesterol were performed as previously described.^{7,24} Serum TNF- α was determined with a rat ultrasensitive EIA (ALPCO, Salem, NH, USA).

Statistical analyses

Statistical significance was calculated using a two-tailed paired Student's *t*-test analysis or one-way analysis of variance. *P* values less than 0.05 were considered significant.

Results

Metabolic profile of TNF- α infusion in hamsters

Normal, chow-fed hamsters were used to perform Triton treatment following four hours of TNF- α infusion. Serum TNF- α concentration significantly increased after four hours of TNF- α infusion compared with the controls (375 ± 34 versus 17 ± 1 pg/mL). The TG levels were significantly increased by Triton WR-1339 treatment after two hours fat feeding, compared with baseline levels in control hamsters (0.9 ± 0.05 [baseline] versus 12.3 ± 0.4 mmol/L [postprandial], *P* < 0.001). TNF- α significantly increased postprandial TG levels compared with controls (18.9 ± 0.9 mmol/L, *P* < 0.05). The cholesterol levels were also notably higher after Triton WR-1339 and fat loading, compared with baseline in control hamsters (2.0 ± 0.1 [baseline] versus 3.9 ± 0.1 mmol/L [postprandial], *P* < 0.001). There was a trend for TNF- α -treated hamsters to have higher cholesterol levels, but the difference was not significant (*P* = 0.11). TNF- α did not significantly affect blood glucose and insulin levels (data not shown).

TNF- α infusion increases the accumulation of chylomicron and VLDL₁-apoB48-containing lipoproteins after fat loading

The serum chylomicron-apoB48 increased in saline and TNF- α -treated hamsters, compared with baseline following Triton-WR1339 treatment (Figure 1a, *P* < 0.001 for both). There was a significantly higher accumulation of serum chylomicron-apoB48 in the TNF- α -treated group, compared with saline controls after two hours fat load (Figure 1a). VLDL₁-apoB48 was 89% overexpressed in TNF- α -treated hamsters at two hours fat load time point compared with the control (Figure 1b); at the baseline, the VLDL₁-apoB48 particles were similar between two groups (data not shown). Mean VLDL₂-apoB48 did not change significantly after TNF- α treatment.

Ex vivo effect of TNF- α on inflammation signaling pathway mRNA in enterocytes

To determine whether TNF- α by itself modifies intestinal enterocyte gene expression, we compared intestinal enterocytes exposed to TNF- α for different time points (0, 0.5, 2 and 4 h). Figure 2a shows Tnf mRNA levels increased 1.5-fold at two hours and 1.9-fold after four hours of TNF- α treatment. Additional key mediators of the inflammatory response, including Il1 α mRNA expression increased 1.4- and 1.9-fold at two and four hours (Figure 2b, *P* < 0.05). Similarly, Il1 β mRNA expression increased 1.8- and 1.6-fold after two and four hours TNF- α treatment, compared with the controls (Figure 2c, *P* < 0.05). TNF- α also increased Il6 gene expression, 2.2-fold to 1.5-fold between 0.5 and 4 h.

Ex vivo effect of TNF- α on insulin signaling pathway in enterocytes

In previous experiments, we demonstrated that TNF- α infusion decreased the phosphorylation of Ir, Irs1 and Akt after an insulin clamp.⁷ To evaluate whether TNF- α disturbs gene expression of the insulin signaling pathway in primary

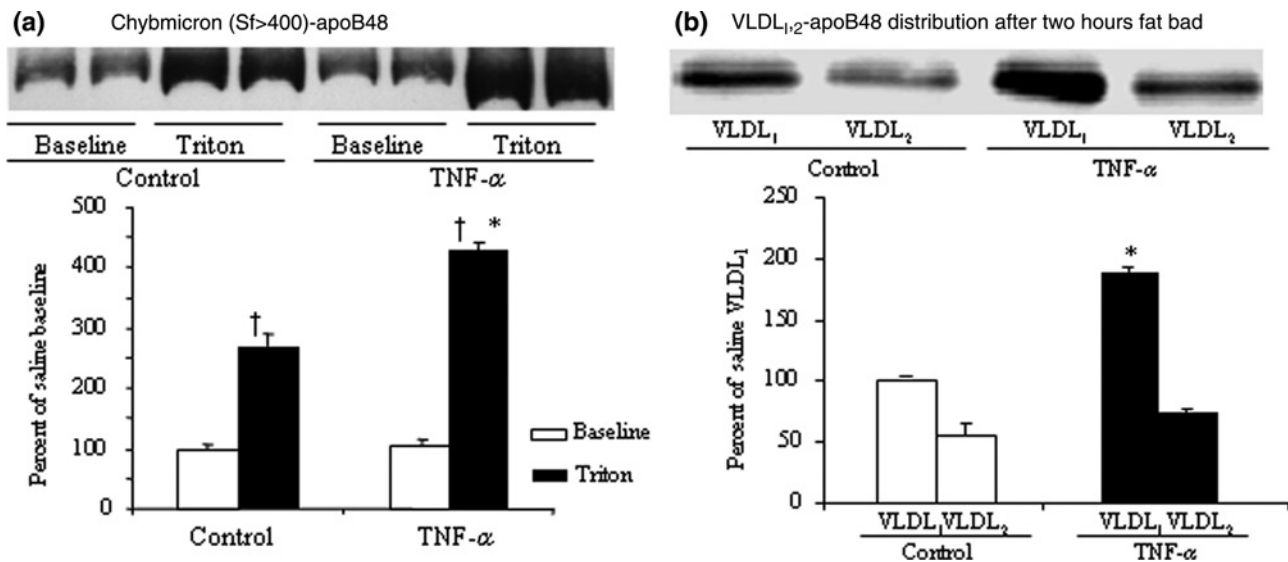


Figure 1 Effect of TNF- α infusion on the circulating apoB48-containing chylomicron and VLDL particles after fat loading. Chylomicron- and VLDL-apoB48 were immunoblotted using anti-hamster apoB primary antibody followed by anti-rabbit horseradish peroxidase second antibody. (a) Representative experiments on chylomicrons in the baseline and two hours fat-loaded state; immunoblots were analyzed using densitometry and expressed as a proportion of baseline. (b) Representative experiments on VLDL-apoB48 particles after two hours fat load; immunoblots were analyzed using densitometry and expressed as a proportion of control VLDL₁. The values given are means $\pm$ SE, ($n = 5$). [†] $P < 0.001$ versus baseline; controls; ^{*} $P < 0.05$ versus controls

enterocytes, TNF- α was added to the media of enterocyte cells and mRNA levels were investigated. Ir gene expression decreased 36%, 28% and 56% at 0.5, 2 and 4 h of TNF- α treatment (respectively). A decrease in Irs1mRNA expression of 40%, 62% and 58% of the controls was also observed between 0.5 and 4 h (Figure 3b). Similarly, as shown in Figure 3c, Irs2 mRNA expression decreased by 66%, 46% and 39% at 0.5, 2 and 4 h, respectively. PI3 k mRNA levels, shown in Figure 3d, decreased by 23%, 35% and 43% at 0.5–4 h. Akt expression shown in Figure 3e, also decreased, 52%, 62% and 75% at 0.5, 2 and 4 h after TNF- α treatment, respectively.

Ex vivo effects of TNF- α on and Cd36, Ppar γ mRNA expression in enterocytes

The maximum expression of Cd36 mRNA levels was at two hours (1.5-fold) and then gradually decreased by four hours

(Figure 4a). TNF- α also significantly enhanced Ppar γ mRNA levels, with increases of 1.6-, 2.0- and 1.7-fold of the controls after 0.5, 2 and 4 h (Figure 4b).

Effects of TNF- α on protein and mRNA expression of Pten, Mtp and Srebp1c in enterocytes

As shown in Figure 5, the Pten protein (a) increased by 0.26-, 0.71- and 1.18-fold after 0.5, 2 and 4 h TNF- α treatment; elevated Pten mRNA levels (b) occurred as early as 0.5 h (1.3-fold), two hours (1.6-fold) and remained increased up to four hours (2.3-fold). We have reported previously that Mtp mRNA and protein were markedly increased by TNF- α .⁷ The time course of the Mtp protein and mRNA is shown in Figures 5c and d, with increases of 21–73% (protein), 33–60% (mRNA) of the controls, at 0.5, 2 and 4 h (respectively). As shown in Figure 5, enterocytes treated with TNF- α had a significantly decreased protein

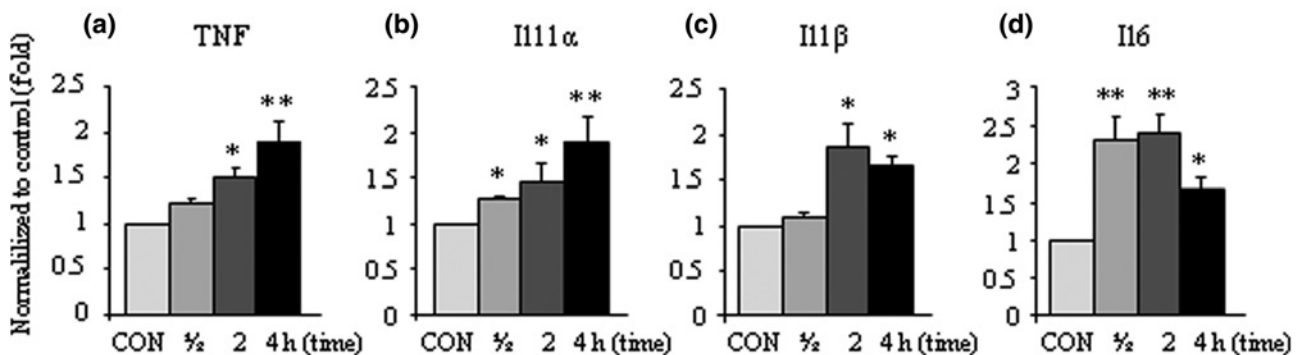


Figure 2 Time course of the effects of TNF- α on the mRNA levels of an inflammatory pathway in primary hamster enterocytes. Panels a–d: TNF- α (a), Il1 α (b), Il1 β (c), Il6 (d). Values are mean $\pm$ SE and are presented as fold of each time's control ($n = 3$). ^{*} $P < 0.05$ and ^{**} $P < 0.01$ versus control

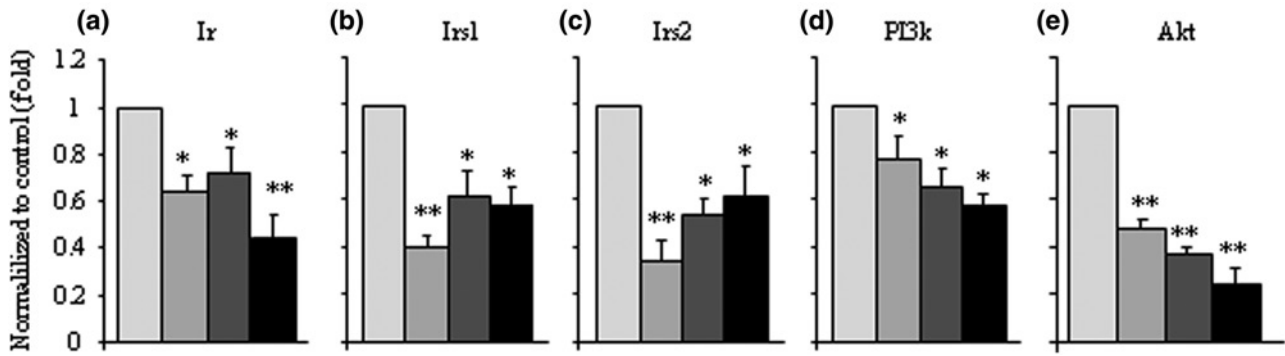


Figure 3 Time course of the effects of TNF- α on the mRNA levels of insulin signaling pathway and Pten in primary hamster enterocytes. Panels a–e: Ir (a), Irs1 (b), Irs2 (c), PI3k (d) and Akt (e). Values are mean $\pm$ SE and are presented as fold of each time's control ($n = 3$). * $P < 0.05$ and ** $P < 0.01$ versus control

of mature and immature forms of Srebp1 compared with control (e1: 97–37% [immature]; e2: 61–31% [mature]); f: Srebp1 mRNA expression decreased 42–64%, after 0.5, 2 and 4 h after TNF- α treatment.

Discussion

TNF- α has been shown to play a key role in mediating insulin resistance as a result of obesity and in numerous animal models of obesity–diabetes syndromes.¹⁶ We demonstrated previously that TNF- α stimulates hepatic VLDL₁-apoB100 overproduction after fat loading.⁸ Here, we observed that TNF- α significantly induced postprandial hypertriglyceridemia and overproduction of intestinal-derived apoB48-containing chylomicrons (TRL fractions) and VLDL₁-particles in the fat-loaded state.

Substantial evidence^{12,25} suggests that insulin regulates the assembly process of VLDL and impaired insulin signaling results in increased VLDL production. The gene overexpression of inflammatory factors, such as Il1, Il6 and TNF, might impair insulin action and reduce insulin signaling efficiency.¹⁶ In the present study, we observed that in TNF- α -treated enterocytes, the mRNA levels of the inflammatory factors, Il1 α and β , Il6 as well as Tnf, increased significantly. TNF- α had a strong stimulatory effect on the expression of several inflammation-related adipokine genes in human adipocytes, including a substantial stimulation of its own expression.^{26,27}

Recently, we reported⁷ that TNF- α infusion not only induces systemic insulin resistance, but also impairs phosphorylation and mass of small intestinal insulin signaling molecules. In our experiments, TNF- α was also found to

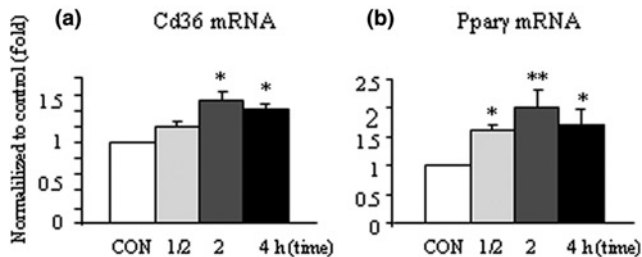


Figure 4 Time course of the effects of TNF- α on the mRNA levels of Cd36 and Ppar γ in primary hamster enterocytes. Panels a–b: Cd36 (a); Ppar γ (b). Values are mean $\pm$ SE and are presented as fold of each time's control ($n = 3$). * $P < 0.05$ and ** $P < 0.01$ versus control

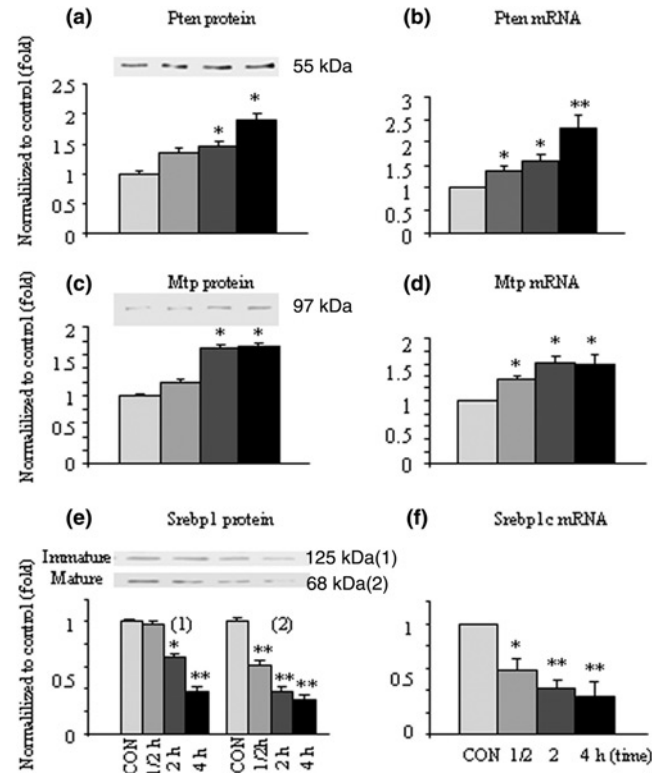


Figure 5 Effects of TNF- α on the mass and mRNA levels of Pten, Mtp and Srebp1c in primary hamster enterocytes. Primary enterocytes were incubated with TNF- α (10 ng/mL) for the indicated times at 37°C, then the cells were washed twice in 2 mL cold PBS, and the cell lysates were prepared as described previously.^{7,24} Panels a and c, the effects of TNF- α treatment on the protein of Pten and Mtp. The sample protein extracts were analyzed by immunoblotting with an anti-Pten antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) or anti-Mtp antibody (BD Bioscience, San Jose, CA, USA). Panels e, the effects of TNF- α treatment on the protein of Srebp1c. Nuclear proteins were analyzed by immunoblotting with an anti-Srebp1c antibody (Santa Cruz Biotechnology). Pten (b), Mtp (d) and Srebp1c (f) mRNA were determined with RT-PCR using cDNA made from 25 ng total RNA as template. Values are mean $\pm$ SE and are presented as fold of each time's control ($n = 3$). * $P < 0.05$ and ** $P < 0.01$ versus control. PBS, phosphate-buffered saline

decrease the mRNA expression of the insulin signaling pathway components including Ir, Irs1, Irs2, PI3 k and Akt in primary enterocytes. Pten's role as an antagonist of the PI3 k/Akt pathway has been documented^{28,29} and is a negative regulator of glucose and lipid metabolism in fructose-fed lean and obese Zucker rats.²⁹ We have also obtained evidence for mass and mRNA overexpression of Pten in the small intestine of fructose-fed, insulin-resistant hamsters, and that insulin treatment inhibits Pten mRNA expression in primary enterocytes (unpublished data). In the fructose-fed hamster model, Federico *et al.*⁹ reported that aberrant intestinal insulin signaling is an important underlying factor in intestinal overproduction of atherogenic apoB48-containing lipoproteins. Our current results suggest that TNF- α can induce Pten expression at protein and mRNA level, which was associated with the impaired mRNA expression of PI3 k/Akt pathway. This may play a crucial role in the overproduction of the intestinal-derived apoB48-containing particles.

Recent evidence has also shown that the transmembrane protein Cd36, a fatty acid transporter, plays an important role in small intestine lipid absorption and chylomicron formation and secretion.³⁰ Streptozotocin-induced diabetic animals³¹ and animals fed a high-fat diet³² showed significant increases in Cd36 mRNA in the intestine. Our data suggest that TNF- α stimulates Cd36 expression at the mRNA level in the primary enterocytes. Ppar γ is a lipid sensor that regulates lipid metabolism²⁰ and plays an important role in the regulation of CD36 expression.³³ A previous study reported that TNF- α decreases Ppar γ mRNA expression in adipocytes.³⁴ In contrast, we observed that TNF- α induced Ppar γ expression. Our results are consistent with the recent report that TNF- α enhanced Ppar γ gene expression in rabbit subcutaneous adipocytes.³⁵ These conflicting observations may relate to differences in experimental conditions (i.e. cell type, treatment time, etc.).

Mtp is essential for the assembly of VLDL in the liver and the chylomicrons in the intestine.³⁶ The production of apoB-containing VLDL and Mtp mRNA levels are acutely regulated by insulin in HepG2 cells.³⁷ Intestinal expression of Mtp is increased in diabetic rats.³⁸ We reported that Mtp protein mass and mRNA were markedly increased by TNF- α .⁷ In this study, we observed that TNF- α stimulated Mtp protein and mRNA expression as soon as 0.5 h. The up-regulation of Mtp may be responsible for the production of increased numbers of apoB48-containing particles.³⁹ We also found that enterocytes treated with TNF- α had significantly decreased mass and mRNA expression of Srebp1c, an important regulator of lipogenesis that has a crucial role in the regulation of TG accumulation in the liver.⁴⁰ This is consistent with previous studies reporting that mRNA levels of Srebp1c were decreased by TNF- α treatment of hepatocytes⁸ and adipocytes.⁴¹ Interestingly, this appears to be in contrast to increased Srebp1c protein⁹ and mRNA levels (unpublished data) in small intestines of fructose-fed hamsters, and Srebp1c mRNA levels in livers of type 2 diabetic mice.⁴² It is reasonable that, although acute treatment with TNF- α reduces Srebp1c expression, chronically increased circulating levels of TNF- α may be associated with increased Srebp1c mRNA expression.

Taken together with previous studies,^{7,8,14,15,43} we propose a mechanism whereby TNF- α influences intestinal apoB48-containing lipoproteins and systemic dyslipidemia in the insulin-resistant state. Systemic elevation of TNF- α causes both local intestinal and systemic insulin resistance and induces the expression of intestinal inflammatory components and impairs insulin and lipoproteins pathways. TNF- α stimulates the overproduction of intestinal-derived apoB48-containing particles, which enhances the overproduction of hepatic lipoproteins and delays the clearance of the hepatic-derived apoB100-containing lipoproteins.^{14,15,43} These findings help us better understand TNF- α 's potential target genes and signaling pathways in the overproduction of small intestinal-derived apoB48-containing lipoproteins. Our data provide mechanistic insights that systemic elevation of TNF- α stimulates the postprandial overproduction of intestinal apoB48-containing chylomicron and VLDL₁ particles by disturbing intestinal inflammatory, lipoprotein and insulin signaling pathways.

ACKNOWLEDGEMENTS

The study was supported by Integrity Nutraceuticals International and USDA'S CRADA NO. 58-3K95-7-1184. We acknowledge Dr Joseph F Urban, Jr, and Dr Allison A Yates for critically reading the manuscript.

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(Received May 19, 2009, Accepted July 25, 2009)