Leptin, skeletal muscle lipids, and lipid-induced insulin resistance

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First published May 9, 2007; doi:10.1152/ajpregu.00133.2007.—Leptin-induced increases in insulin sensitivity are well established and may be related to the effects of leptin on lipid metabolism. However, the effects of leptin on the levels of lipid metabolites implicated in pathogenesis of insulin resistance and the effects of leptin on lipid-induced insulin resistance are unknown. The current study addressed the pathogenesis of insulin resistance and the effects of leptin on lipid metabolism. Of these, leptin-induced stimulation of fatty acid oxidation and decreases in circulating and tissue levels of triglyceride (TG) are best described (11, 25, 26, 36, 37, 43, 49, 55). In addition to a role in the regulation of lipid metabolism, the beneficial effects of leptin on insulin sensitivity are well established. Thus insulin resistance in leptin-deficient states (5, 11, 16, 29, 38, 43, 49, 52). Arising from these observations, it has been proposed that the beneficial effects of leptin on lipid metabolism may contribute to improvements in insulin sensitivity, a hypothesis supported by studies demonstrating detrimental effects of lipids on insulin action (2, 7, 12, 20, 22, 27, 31, 39, 41, 58, 62).

In humans and rodents there is a strong negative correlation between plasma and tissue TG levels and insulin sensitivity (22, 31, 34, 51). Furthermore, acute infusions of lipid induced skeletal muscle insulin resistance in vivo (2, 6, 7, 12, 15, 20, 27, 62), and fatty acids induce insulin resistance in skeletal muscle cell lines in vitro (13, 48, 53). In addition to TG, a number of other lipid metabolites have been proposed to contribute to the detrimental effects of lipids on insulin sensitivity in muscle. In short, there is evidence (1, 13, 47, 48, 57, 59, 62) that increased levels of diacylglycerol (DAG) and/or ceramide contribute to decreased insulin action, effects that possibly involve activation of the novel protein kinase C-θ (PKCθ) and/or inhibition of Akt (4, 13, 20, 27, 30, 47, 48, 57, 62). However, the effects of leptin on muscle ceramide and DAG levels and insulin signaling pathways are unknown. Furthermore, the effects of leptin on lipid-induced insulin resistance have not been addressed directly, since previous studies have simply demonstrated a correlation between the effects of leptin on insulin action and lipid metabolism and were performed in models of preexisting insulin resistance and hyperlipidemia (ob/ob mouse, diet-induced obesity, and lipodystrophy). Thus the primary goals of the current study were to address these issues. The data demonstrate that leptin-induced improvements in insulin sensitivity are associated with lowered skeletal muscle TG levels, increased skeletal muscle insulin signaling, and decreased levels of PKCθ, but not with decreases in skeletal muscle levels of DAG and ceramide. Furthermore, leptin protects against insulin resistance induced by an acute lipid infusion.

MATERIALS AND METHODS

Animal Care and Maintenance

Male Wistar rats weighing 200–280 g were purchased from Charles River Laboratories (Wilmington, MA). Animals were individually housed in environmentally controlled conditions on a constant 12:12-h light-dark cycle with free access to food and water. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh and are in accordance with the National Research Council’s Guide for the Care and Use of Laboratory Animals.

Study Design

All studies were performed ~10 days after the insertion of indwelling catheters and 5 days after adenovirus administration in 18- to

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24-h-fasted animals, as described in detail below. Studies measuring insulin sensitivity and skeletal muscle lipid levels were performed in separate groups of animals. To allow comparisons between studies and conditions, assessments of insulin sensitivity and lipid levels were always performed subsequent to a saline or lipid infusion, as described below, except in studies assessing skeletal muscle insulin signaling. In three studies, the effects of hyperleptinemia, or hyperlipidemia combined with hyperleptinemia, on insulin sensitivity and lipid levels (TG, DAG, ceramide) in two skeletal muscles differing in fiber type composition (soleus muscle, a slow-twitch, oxidative muscle composed predominantly of type I muscle fibers, and superficial vastus, a fast-twitch, glycolytic muscle composed predominantly of type II muscle fibers) were evaluated. The effects of hyperleptinemia on skeletal muscle insulin signaling were assessed in separate studies, as described below.

**Animal Surgeries**

Catheters (PE-50, Intramedic; Becton Dickinson, Sparks, MD) were placed into the carotid artery (advanced to the aortic arch) and jugular vein (advanced to the right atrium) 5–10 days before a study as described previously (14). All subsequent studies were performed in animals that achieved at least 90% of presurgery weight.

**Recombinant Adenovirus Administration**

In studies requiring hyperleptinemia, chronically catheterized rats (~5 days after surgery) received a recombinant adenovirus containing the leptin cDNA (1 × 10^{12} particles; HL animals) by tail vein injection as previously described (11). Control animals (CONT) received a recombinant adenovirus containing the Escherichia coli β-galactosidase cDNA (1 × 10^{12} particles). Subsequently, CONT were calorically matched to HL animals to adjust for leptin-induced decreases in food intake, as previously described (11). Studies (lipid/saline infusions, insulin clamps) described below were performed 5 days after adenovirus administration.

**Lipid and Saline Infusions**

In studies requiring the induction of acute hyperlipidemia, overnight-fasted (18–24 h) CONT or HL animals were infused with Liposyn II/heparin (5 ml·kg^{-1}·h^{-1}) and 6 U/h, respectively; Abbott Laboratories, Chicago, IL) for 6 h. Control animals received a saline infusion (5 ml·kg^{-1}·h^{-1}) for a similar period of time. At the end of the infusions, either animals were killed and their tissues (skeletal muscle and blood) isolated for the analysis of lipid levels, or they underwent a hyperinsulinemic clamp as described below.

**Hyperinsulinemic Clamps**

All clamps were performed in 18- to 24-h-fasted HL or CONT animals subsequent to a 6-h saline or lipid infusion as described above. A venous infusion of insulin (Humulin; Eli Lilly, Indianapolis, IN) at 15 mU·kg^{-1}·min^{-1} was begun in conjunction with a variable glucose (30%) infusion to maintain plasma glucose concentrations (Glucose II analyzer; Beckman, Fuller, CA) at euglycemia (~110 mg/dl). The insulin infusion rate used ensured that hepatic glucose output was completely suppressed (44). Arterial blood samples (~30 μl) were taken every 8–10 min throughout the clamp, which lasted 90 min. The glucose infusion rate during the final 30 min of the clamp was used as an index of insulin sensitivity (insulin-stimulated whole body glucose disposal), as previously described (2, 7, 14, 20, 34, 40). Total blood volume taken throughout the clamp period did not exceed 5% of total blood volume (approximated from body weight).

**Activation of Insulin Signaling Pathways**

For insulin signaling studies, anesthetized CONT or HL rats were administered a bolus injection of insulin (10 U/kg) via a jugular vein catheter, inserted as described above. Five minutes after administration of the insulin, skeletal muscle was isolated, flash frozen in liquid nitrogen, and stored at −70°C until analysis.

**Skeletal Muscle Analysis**

**DAG and ceramide.** Approximately 30 mg of frozen skeletal muscle were homogenized in 1 ml of ice-cold methanol containing butylated hydroxytoluene (5 μg/ml) as an antioxidant. The methanol homogenate was mixed with 2 ml of chloroform, and lipids were extracted using the method of Folch et al. (17). DAGs and ceramides were phosphorylated from a 50-μl aliquot of the lipid extract by the addition of DAG-kinase (5 μl per sample) and 5 μCi [γ-^32P]ATP according to the method of Preiss et al. (45). Subsequently, ^32P-labeled DAGs and ceramides were separated by thin-layer chromatography (TLC). After completion of the chromatography, the silica plates were exposed to autoradiography film. By using the developed film for orientation, DAGs and ceramides were located on the silica plate and scraped into separate scintillation vials. Scintillation cocktail was added, and the product was counted for 1 min. DAG and ceramide concentrations were calculated as nanomoles per milligram of protein based on DAG and ceramide standards run in conjunction with test samples. This analysis method gives data quantitatively similar to that obtained using high-performance liquid chromatography-fluorescence spectrometry for total ceramide content and, presumably, total DAG content (10). Furthermore, the concentrations of ceramide and DAG reported in this study are similar to those reported using liquid chromatography-tandem mass spectrometry (62) and gas-liquid chromatography (19).

**Triglycerides.** A 200-μl aliquot of extracted lipids was air-dried overnight in a glass sample tube. Subsequently, 40 μl of Triton X-114-methanol (2:1 vol/vol) and 60 μl of tert-butanol were added, and the sample was vortexed. Samples and standards were assayed spectrophotometrically using a commercially available assay kit (Sigma-Aldrich, St. Louis, MO).

**Fatty acid oxidation.** Bilateral whole soleus muscles were isolated from fasted HL and CONT rats and placed in pregressed 37°C Krebs-Ringer-Henseleit buffer containing 2.4% BSA and 0.4 mM [1^-3H]palmitate (1 μCi/ml) for 1 h. Palmitate oxidation was assayed by measuring the quantity of tritiated water released into the medium, as previously described (42, 49). Briefly, at the end of the 1-h incubation, 200 μl of incubation medium was transferred to an open 1.5-ml tube, and the tube was placed into a 20-ml scintillation vial containing 0.5 ml of unlabeled water. The scintillation vial was capped and kept at 50°C for 18 h to allow equilibration of tritiated and unlabeled water. To determine the equilibration coefficient, 200 μl of medium containing a known quantity of tritiated water (10 μCi) were incubated similarly to other samples. After the 18-h incubation, 10 ml of scintillation fluid were added to the vials and the samples were counted.

**Phosphatidylinositol 3-kinase activity.** Insulin receptor substrate (IRS)-1-associated phosphatidylinositol 3-kinase (PI3-kinase) activity was measured as previously described (26). Briefly, 3 μg of αIRS-1 antibody (Upstate Biotechnology, New York, NY) was incubated with 250 μg of protein for 2 h, followed by the addition of protein A-Sepharose for 1.5 h (Amersham Biosciences). Subsequently, the immunocomplexes were incubated for 10 min at 22°C with phosphatidylinositol and [γ-^32P]ATP. ^32P-containing phosphatidylinositol (3)-phosphate [PI(3)P] was separated by TLC exposed to autoradiographic film and quantified by densitometry.

Akt, glycogen synthase kinase-3α, fatty acid transporters, fatty acid binding proteins, acetyl Co-A carboxylase, and PKCζ. Protein extracts and/or membrane fractions were prepared from ~100 mg of skeletal muscle (gastrocnemius muscle). Total Akt and phosphorylated Akt (Ser473), total glycogen synthase kinase-3α (GSK3α) and phosphorylated GSK3α (Ser21), phosphorylated acetyl Co-A carbox-
Enzyme (ACC; Ser79), total fatty acid transporter (FAT)/CD36, plasma membrane fatty acid binding protein (FABPpm), and membrane and cytosolic PKC levels were determined using standard immunoblot protocols described previously (8, 9, 25).

Statistical Analysis

All data are means ± SE. Statistical significance was determined by unpaired t-test using SPSS (Chicago, IL) statistical software. Significance was assumed at P < 0.05.

RESULTS

Leptin-Induced Improvements in Insulin Sensitivity are Associated With Lowered Skeletal Muscle TG, Increased Ceramides, and Unaltered DAG Levels

Previously, our group demonstrated in obese rats (11) that leptin-induced improvements in skeletal muscle insulin sensitivity are correlated with decreased skeletal muscle TG levels. To further address the association of altered skeletal muscle lipid metabolism with leptin-induced improvements in insulin sensitivity, we determined the effects of 96 h of hyperleptinemia (HL: 57.8 ± 3.9 ng/ml vs. CONT: 1.3 ± 0.2 ng/ml) in lean rats on the skeletal muscle levels of lipids implicated in decreasing insulin action. In all experiments, CONT were calorically matched to HL animals during the 4 days preceding an experiment (HL: 12.8 ± 1.7 g/24 h vs. CONT: 12.3 ± 1.1 g/24 h, an ∼40% decrease in daily food intake). There were no statistical differences between HL and CONT animals in body weight, fasting plasma glucose level, or plasma insulin concentration on the day of experiments (data not shown). During the clamp, insulin was infused at a rate of 15 mU-kg⁻¹-min⁻¹ to suppress hepatic glucose output (44), thus ensuring that the glucose infusion rate represented alterations in insulin-stimulated glucose disposal (2, 7, 20, 34, 40), predominantly in skeletal muscle. As expected, the glucose infusion rate required to maintain euglycemia was increased in HL animals compared with CONT (Fig. 1). In soleus muscle, a slow-twitch, oxidative muscle composed predominantly of type 1 fibers, and superficial vastus, a fast-twitch, glycolytic muscle composed predominantly of type 2 muscle fibers, TG content was decreased in HL animals compared with CONT (Fig. 2, A and B). Surprisingly, ceramide levels were increased, whereas DAG levels were unaltered by hyperleptinemia in both muscles (Fig. 2, A and B).
Leptin Protects Against Insulin Resistance and Alterations in Skeletal Muscle TG, Ceramide, and DAG Levels Induced by Acute Hyperlipidemia

The detrimental effects of acute hyperlipidemia on skeletal muscle insulin sensitivity are well described (7, 12, 24, 33). As such, this model is ideal for directly assessing the capacity of leptin to protect against the effects of lipids on insulin action. As expected, the glucose infusion rates required to maintain euglycemia were decreased in animals receiving a 6-h lipid infusion (LIP) compared with saline-infused (CONT) animals (Fig. 3). These changes in insulin sensitivity were associated with increases in soleus muscle DAG and ceramide levels and decreases in TG in LIP animals compared with CONT (Fig. 4A), in good agreement with the previous study of Yu et al. (62). A similar lipid profile was observed for ceramide and DAG in superficial vastus, but TGs were unaltered in this muscle (Fig. 4B). We next determined the effects of leptin on hyperlipidemia-induced insulin resistance. The glucose infusion rate required to maintain euglycemia was not different in HL animals receiving a lipid infusion (HL-LIP) compared with HL animals receiving a saline infusion (HL-CONT), demonstrating that HL protects against the detrimental effects of lipids on insulin action (Fig. 5). Furthermore, soleus DAG, ceramide, and TG levels subsequent to a lipid infusion (HL-LIP) were similar to levels observed subsequent to a saline infusion (HL-CONT) (Fig. 6A). A similar pattern was observed in superficial vastus, although DAG levels were lower in HL-LIP compared with HL-CONT (Fig. 6B).

Leptin Increases Insulin-Stimulated Akt and GSK3β Activity in Skeletal Muscle

Our group (11) and others (3, 43, 54, 60, 61) have previously demonstrated that leptin increases insulin-stimulated glucose uptake into skeletal muscle. In the current study we assessed the effects of leptin on the capacity of insulin to activate the PI3-kinase-Akt-GSK3β signaling axis in skeletal muscle. In HL, IRS-1-associated PI3-kinase activity was increased, although the increase did not reach statistical significance (Fig. 7A, $P = 0.06$, $n = 10$). However, insulin-stimulated activation of Akt was $1.3 \pm 0.1$ times greater compared with CONT animals (Fig. 7B, $P = 0.02$), whereas phosphorylation of GSK3β, a target of Akt activity, was increased $2.1 \pm 0.4$ times in HL compared with CONT animals (Fig. 3C, $P = 0.02$). We concluded from these data that leptin increases responsiveness of the insulin-signaling pathway to insulin in skeletal muscle.
Skeletal Muscle Fatty Acid Binding Protein/Transporter Levels and ACC Phosphorylation are Unchanged, but PKC/H9258 Levels are Decreased, by Hyperleptinemia

We next assessed the effects of leptin on a number of biochemical mechanisms that may play a role in altered lipid metabolism and/or increased insulin sensitivity. Fatty acid entrance into the cell may require plasma membrane fatty acid binding proteins (FABPpm) and fatty acid transporters (FAT/CD36). Furthermore, it has been reported that a chronic leptin infusion decreases FABPpm and FAT/CD36 (56). However, in the current study no differences in skeletal muscle FABPpm and total FAT/CD36 content were observed between HL and CONT animals (Fig. 8, A and B).

We next determined the effects of chronic HL on ACC phosphorylation and fatty acid oxidation in skeletal muscle. Surprisingly, exogenous palmitate oxidation was not increased in the isolated skeletal muscle (Fig. 8C), and ACC phosphorylation was not increased (Fig. 8D) in muscle taken from HL compared with CONT animals. However, this was most likely due to the measurements being performed ex vivo, since Steinberg et al. (55) reported similar results in the isolated rat muscle, and previous studies have demonstrated stimulatory effects of leptin on skeletal muscle fatty acid oxidation in vivo (35, 49).

It has been proposed that increased activity/expression of PKC\(\theta\), possibly mediated by DAG, is a contributing mechanism to the development of lipid-induced skeletal muscle insulin resistance (4, 20, 62). Thus we thought it possible that leptin might decrease PKC\(\theta\) activity. Subsequent to lipid infusions, both cytosolic and membrane PKC\(\theta\) levels in skeletal muscle were reduced \(-30\%\) (both \(P < 0.05\)) in HL compared with CONT animals (Fig. 9), suggesting one potential biochemical mechanism for the protective effects of leptin against lipid-induced insulin resistance.

**DISCUSSION**

The purpose of the current study was to gain a greater understanding of the effects of leptin on levels of skeletal muscle lipids implicated in the pathogenesis of insulin resistance, to assess the capacity of leptin to protect against the detrimental effects of lipids on insulin action, and to begin to understand the biochemical basis of leptin action on insulin sensitivity. The data demonstrate that leptin-induced improvements in insulin sensitivity are not clearly associated with...
decreased levels of skeletal muscle lipids implicated in the pathogenesis of insulin resistance, whereas insulin resistance induced by acute hyperlipidemia is prevented by leptin. Potential biochemical mechanisms mediating these effects include leptin-induced increases in the responsiveness of the skeletal muscle insulin signaling pathway to insulin and reductions in the levels of skeletal muscle PKC, a kinase implicated in reducing insulin sensitivity.

The association between leptin effects on lipid metabolism and leptin effects on insulin action suggests that the latter effects may be mediated by decreasing the levels of lipid metabolites such as TG, ceramide, and DAG that have been...
implicated in the pathogenesis of lipid-induced insulin resistance (1, 13, 47, 48, 57, 59, 62). Indeed, leptin has potent lowering effects on plasma and tissue TG levels, but it is thought that TGs per se are unlikely to play a direct mechanistic role in altering insulin action. Rather, the TG-lowering effects of leptin are thought to be a surrogate marker for alterations in other lipid metabolic pathways that may alter insulin action. Thus it was somewhat surprising in the current study that whereas leptin increased insulin sensitivity, and the increases were associated with decreases in TG levels in both slow-twitch, oxidative (soleus) and fast-twitch, glycolytic (superficial vastus) muscle fibers, there were no corresponding decreases in the levels of either ceramide or DAG. Indeed, ceramide increased in both muscle fiber types examined in hyperleptinemic animals, whereas DAG was unchanged. Thus, under the conditions examined (hyperleptinemia in lean animals), the beneficial effects of leptin on insulin sensitivity occur independently of alterations in the levels of these lipid metabolites.

Previous studies in ob/ob and lipodystrophic mice and in diet-induced obese rats correlated leptin-induced improvements in insulin sensitivity with improvements in plasma and tissue TG profile. This led us to ask whether leptin could prevent insulin resistance induced by hyperlipidemia, thereby addressing the relationship between lipid and leptin effects on insulin action. Importantly, in the presence of hyperleptinemia, the detrimental effects of lipids on insulin action were abolished. Arising from this observation is the issue of the mechanism of the protective effects of leptin. One possibility is that leptin acts by preventing the accumulation of DAG and ceramide induced by hyperlipidemia, since neither DAG nor ceramide was increased in lipid-infused compared with saline-infused hyperleptinemic animals, whereas both metabolites were increased by a lipid infusion in animals with basal leptin concentrations. However, as discussed above, decreases in DAG or ceramide are not correlated with the effects of leptin on insulin action in lean animals. It is possible that leptin effects on other lipid metabolic pathways are involved in leptin-induced increases in insulin sensitivity. Of interest in this regard are the observations that increased fatty acid oxidation in L6 myotubes achieved by overexpression of carnitine palmitoyltransferase-1 (CPT-1) protects these cells from the detrimental effects of fatty acids on insulin action without altering ceramide or DAG levels (42). Also, in exercise training (18, 46) there is an increase in insulin sensitivity that correlates with increased skeletal muscle oxidative capacity but not with TG levels, which are paradoxically increased. In the current study we did not observe leptin-induced increases in fatty acid oxidation or ACC phosphorylation, although previous studies have suggested that there is a stimulatory effect of leptin on fatty acid oxidation in skeletal muscle (35, 49), possibly mediated by an inactivation of ACC and relief of inhibition of CPT-1. However, it is possible that the model we used (i.e., the isolated muscle) explains the current data, since previous studies were performed in vivo (35, 49) or in isolated muscles receiving electrical stimulation (55). Indeed, in this latter study (55), the authors reported that fatty acid oxidation was not increased by leptin in nonstimulated muscles, the conditions that were used in the current study. One conclusion that can be made is that leptin-induced genomic changes that

![Fig. 9. Effect of leptin on cytosolic and membrane-associated PKCα. Membrane-associated and cytosolic PKCα contents of gastrocnemius muscle were measured from HL and CONT animals. A and B, top, shows representative autoradiographs of cytosolic and membrane-associated PKCα, respectively. A and B, bottom, shows quantification, as measured using scanning densitometry, of the total data set. C: a ratio of PKCα membrane fraction divided by the total. Results are means ± SE; n = a minimum of 6 muscles per group. Statistical significance is indicated.](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00106.2006.supp)
would result in enhanced fatty acid oxidation are not occurring and that sympathetic innervation may be required to observe leptin-induced increases in fatty acid oxidation.

We have demonstrated that the capacity of insulin to activate elements of the insulin-signaling pathway in skeletal muscle is improved by leptin, suggesting one biochemical mechanism underlying the beneficial effects of leptin on insulin action. It is also clear that the increases in the responsiveness of the insulin signaling pathway are most closely associated with decreases in skeletal muscle TG but are not related to decreases in ceramide or DAG. However, it is unknown how decreases in TG would improve insulin signaling. Indeed, it remains a possibility that this association is purely correlative and that the TG level may reflect increases in the activity of other unknown lipid metabolic pathways or fatty acid oxidation, as discussed above. Alternatively, it is important to consider that other mechanisms that may be unrelated to leptin effects on lipid metabolism may mediate leptin effects on insulin signaling. An interesting observation was that insulin-stimulated IRS-1-associated PI3-kinase activity was not increased in HL animals, despite increases in Akt and GSK3α phosphorylation. This was somewhat surprising given that Akt is a proximal downstream target of PI3-kinase activity. Furthermore, a recent study suggested that leptin inhibits insulin signaling at the level of IRS-1 (23), demonstrating that there is a potentially complex relationship between leptin-induced increases in insulin sensitivity and leptin effects on insulin signaling.

Several studies have demonstrated a relationship between increased activation of PKCθ and insulin resistance. Thus, in response to a lipid infusion in rodents, membrane-associated PKCθ, considered to be the active form of this kinase, is increased, and there is a corresponding decrease in the levels of cytosolic PKCθ (62). Similarly, in obesity, levels of skeletal muscle PKCθ are increased (28). Furthermore, PKCθ-deficient mice (32) are protected against the effects of acute hyperlipidemia on insulin action. In the current study we have demonstrated that both cytosolic and membrane-associated PKCθ are decreased in hyperleptinemic compared with control animals. Thus a potential mechanism of beneficial effects of leptin on insulin action is to decrease PKCθ. The mechanism by which leptin mediates a reduction in PKCθ is unknown but may be related to effects of leptin on lipid metabolism.

In conclusion, the present study demonstrates that leptin-induced improvements in insulin sensitivity cannot be clearly associated with alterations in skeletal muscle lipid levels. There is an association between leptin effects on insulin action and leptin effects on skeletal muscle TG levels, but this association does not extend to the levels of DAG and ceramide. Under conditions of acute hyperlipidemia, leptin protects against the deleterious effects of lipids on insulin action. Leptin increases the responsiveness of skeletal muscle to insulin, as assessed by activation of Akt and inhibition of GSK3α, and decreases the levels of PKCθ, which has been implicated in the pathogenesis of lipid-induced insulin resistance.

REFERENCES


