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Metabolism Clinical and Experimental 60 (2011) 438 – 443
Metabolism
Clinical and Experimental
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Leptin increases skeletal muscle lipoprotein lipase and postprandial lipid metabolism in mice

William T. Donahoo[a], Nicole R. Stob[a], Stefen Ammon[a], Nancy Levin[b], Robert H. Eckel[a,*]

[a]*Division of Endocrinology, Metabolism, and Diabetes, University of Colorado Denver, 12801 East 17th Avenue, Mail Stop 8106, Aurora, CO 80045, USA*
[b]*CovX Research, 9381 Judicial Dr, Suite 200, San Diego, CA 92121, USA*

Received 5 August 2009; accepted 23 March 2010

Abstract

The ability of leptin to preserve lean tissue during weight loss may be in part due to differences in nutrient partitioning. Because lipoprotein lipase (LPL) plays a key role in partitioning lipid nutrients, this study was conducted to test the hypothesis that leptin would modify the tissue-specific regulation of LPL and result in increased lipid oxidation and decreased storage. The effects of daily intraperitoneal leptin injections (2 mg/kg body weight) over 2 weeks on LPL activity and postprandial lipid metabolism were tested in both wild-type (WT), leptin-deficient *ob/ob* obese mice and mice pair fed to the leptin-treated mice. On the experimental day, mice were given food by gavage, blood was drawn periodically, and adipose tissue and skeletal muscle were harvested for measurements of LPL activity at 240 minutes. After 2 weeks of leptin administration, skeletal muscle LPL (SMLPL) activity was increased in leptin-treated compared with pair-fed ($P = .012$) and WT ($P = .002$) mice. There was no effect of leptin or pair feeding on postprandial adipose tissue LPL activity. In *ob/ob* mice, leptin treatment normalized the decrease in postprandial free fatty acid concentration ($P = .066$). Leptin had no effect on either the area under the triglyceride (TG) excursion or the integrated area under the TG excursion in WT mice. In *ob/ob* mice, however, the TG excursion was lower in the leptin-treated than the pair-fed mice by area under the TG excursion ($P = .012$) and was lower than in the WT mice by integrated area under the TG excursion ($P = .027$). As expected, 2 weeks of leptin treatment decreased body weight in both the WT and *ob/ob* mice (−2.6% and −10.4%, respectively). Leptin treatment increased SMLPL, an effect that may have contributed to the leptin-induced weight loss. The leptin-induced decreased postprandial TG excursion in *ob/ob* mice suggests that leptin acts to augment clearance of postprandial TG-rich lipoprotein lipid and that this increase may in part be secondary to the increased activity of SMLPL. The trend for decreased postprandial free fatty acid may indicate that leptin decreases adipose tissue lipid stores without increasing lipolysis.
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1. Introduction

Leptin is an adipocyte-derived hormone with both central and peripheral effects on energy metabolism [1]. When leptin is administered exogenously to rodents, it acts as an anorectic agent and decreases food intake. However, in contrast to weight loss by caloric restriction that causes loss of both adipose tissue and muscle mass, leptin exerts actions that result in the loss of adipose tissue with the preservation of lean tissue [2,3]. However, when adipose tissue increasingly accumulates and obesity develops, leptin levels rise, suggesting leptin resistance [4,5].

Lipoprotein lipase (LPL) is the primary mechanism for the hydrolysis of triglyceride-rich lipoprotein triglycerides (TGs) providing resultant fatty acids to tissues [6]. Lipoprotein lipase thus plays a key role in partitioning lipid nutrients into either adipose tissue for storage or skeletal muscle for oxidation. There is substantial evidence that LPL has an important role in postprandial lipid metabolism. Jeppesen et al [7] have shown that measurements of LPL in postheparin plasma are highly associated with the clearance of postprandial lipids. In addition, postprandial lipid metabolism is impaired in LPL deficiency, including patients with heterozygous LPL deficiency, a setting in which fasting lipids and lipoproteins are relatively normal [8].

Conflicts of interest: N Levin was employed by Amgen at the time of the study and is currently an Amgen stock owner.

* Corresponding author. Tel.: +1 303 724 3923; fax: +1 303 724 3924.
E-mail address: robert.eckel@ucdenver.edu (R.H. Eckel).

0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2010.03.016

The preservation of skeletal muscle mass in the setting of leptin-induced weight loss is likely due to increased energy expenditure, but may also be due to differences in nutrient partitioning caused by leptin. Given the role of LPL in nutrient partitioning, this study was conducted to test whether leptin-induced weight loss would be accompanied by a change in the tissue-specific expression of LPL that would favor lipid oxidation over storage, that is, an increased ratio of skeletal muscle LPL (SMLPL) to adipose tissue LPL (ATLPL). Because much of nutrient partitioning occurs in the postprandial state, the effects of leptin on LPL were tested after a mixed meal. Finally, because preliminary data have suggested that leptin decreases postprandial TG excursion [9,10] we examined the impact of leptin on TG excursion after the meal.

2. Methods

Two weeks of daily leptin injections were given, and the effects on LPL activity and postprandial TG excursion were tested. In addition, to test the effect in a lean animal as well as an obese leptin-sensitive animal, both lean (wild type = C57/Bl6J ob^+/ob^+) and obese leptin-deficient (*ob/ob* = C57Bl6J ob^-/ob^-) mice were used.

2.1. Experimental animals and procedure

Studies were conducted in accordance to protocols approved by institutional animal care and use committees (University of Colorado Denver). Female C57BL/6J *ob/ob* and WT C57BL/6J or lean littermates of C57BL/6J *ob/ob* mice were used. Animals were 11.4 ± 0.1 weeks of age. All mice were on a 12-hour light/12-hour dark cycle.

Thirty animals from each strain (10 to receive leptin, 10 to receive saline, and 10 pair fed to the leptin-treated mice) were used. Animals were maintained on standard ad libitum chow throughout the study and had free access to water. Mice treated with leptin were given 2 mg/kg current body weight intraperitoneally daily between 2:00 and 4:00 PM. The saline-treated group received a daily injection of isotonic sodium chloride solution of a volume to match the leptin-treated mice. The amount of food eaten by the leptin-treated mice was calculated daily, and that amount was given to the pair-fed mice the following day. The daily injections and pair feedings were carried out over a 2-week period.

On the evening before study, food was removed from the cages, although mice continued to have free access to water. On the morning of the study, the mouse was lightly anesthetized with Metofane (Schering Plough, Union, NJ); and baseline blood (50 μL) was collected by retroorbital bleed. Mice were then given 1 mL of a mixed meal (as described below) by gastric lavage. Blood was drawn at 60, 120, and 180 minutes by retroorbital bleed (50 μL per time point). At 240 minutes, the mice were anesthetized with Avertin (St. Louis, MO) (~32 mg), 200 μL of blood was obtained from a catheter placed into the inferior vena cava, and mice were killed by cervical dislocation. Blood at all time points was used for measurements of TG; and blood at the initial and final time points were used to assess plasma levels of leptin, glucose, and free fatty acid (FFA) [10]. Adipose tissue was harvested from the gonadal depot, and skeletal muscle was harvested from the gastrocnemius and soleus muscles for determination of LPL activity.

The composition of the mixed meal was 6 g butter + 6 g sunflower oil + 10 g nonfat milk + 10 g sugar. The macronutrient content was 60% fat (37% saturated, 27% monounsaturated, and 36% polyunsaturated), 20% protein, and 20% carbohydrate.

2.2. Serum and tissue assay

Plasma insulin was measured by radioimmunoassay (Linco Research, St Louis, MO) with a sensitivity of 0.02 ng/mL. Plasma leptin was measured at Amgen (Thousand Oaks, CA) using a modification of the radioimmunoassay developed by Linco with a limit of detection is 0.5 ng/mL. The intraassay coefficient of variation (CV) was less than 5%, and the interassay CV was less than 4.5%. Plasma FFAs were measured using the enzymatic methodology from Wako Chemicals (Richmond, VA); and the intraassay and interassay CVs were 5.6% and 1.1%, respectively. Plasma TGs were also done enzymatically (Olympus America, Melville, NY) with intraassay and interassay CVs of 2.2% and 0.8%, respectively.

Lipoprotein lipase activity was measured as previously described ([11] 1986, p259-273). Briefly, adipose tissue or skeletal muscle (40-45 mg per sample) was minced in cold Krebs-Ringer phosphate buffer; and then the lipase was released from tissue with heparin (2 μg/mL). An aliquot of the heparin-released lipase was then incubated with ^{14}C-triolein–labeled lecithin/triolein substrate, and the ^{14}C-oleate was separated from the substrate by the addition of an organic mixture (chloroform, methanol, heptane) and subsequent isolation of the aqueous phase. The extracted FFA were counted in a β-scintillation counter. Data are expressed as nanomoles of FFA released per minute per 10^6 cells (adipose tissue) or per gram of muscle (skeletal muscle).

2.3. Data analysis

All data are presented as mean ± SE. Statistics were run on either SigmaStat 2.0 (Jandel Scientific, San Raphael, CA) or SAS (Cary, NC). Age, weight, final glucose, and final FFA were initially compared by 2-way analysis of variance (ANOVA) using type (*ob/ob* vs wild type) and leptin treatment (yes vs no) as the independent variables. This was followed by an unpaired Student *t* test if significance was established by ANOVA. The effect of gavage on glucose and FFA was analyzed by a paired *t* test. The effect of treatment on LPL activity was analyzed by unpaired *t* test comparing leptin-treated animals to pair-fed or WT controls. The data for the TG excursion were analyzed in multiple ways including area under the curve (AUC), integrated area under

the curve (IAUC), final TGs, change in TGs ($T = 240 - 0$ minute), and TGs at 100 minutes (peak). Each of these comparisons was analyzed by 2-way ANOVA followed by unpaired Student t test if significance occurred with ANOVA. Significance is set as $P < .05$. Groups are reported as WT+ (wild-type animals treated with leptin), WT− (wild-type animals treated with saline), *ob/ob*+ (o*b/ob* animals treated with leptin), *ob/ob*− (*ob/ob* animals treated with saline), and *ob/ob* PF (*ob/ob* animals that were pair fed).

3. Results

The characteristics of the mice treated with leptin daily for 2 weeks are presented in Table 1. As expected, there was both a group and treatment effect ($P < .001$) on body weight. In addition, there was a group ($P < .001$) and treatment ($P = .009$) effect on final plasma glucose concentration. There was also a group effect ($P = .005$) and a trend for a treatment effect ($P = .066$) on final plasma FFA concentration.

Fig. 1 shows the effect of 2 weeks of leptin treatment on LPL activity. There was no effect of leptin or pair feeding on the postprandial adipose tissue LPL activity (Fig. 1A, B). In contrast, there was a higher SMLPL in WT mice treated with leptin compared with either pair-fed ($P = .012$) or untreated WT mice ($P = .002$, Fig. 1A). There was a similar trend in the *ob/ob* mice, with SMLPL trending higher in leptin-treated compared with the saline-treated mice ($P = .08$, Fig. 1B).

Fig. 2 shows the effect of leptin administration on plasma FFA before and after a meal. There was a decrease in plasma FFA with the meal in WT ($P = .03$) and leptin-treated mice ($P = .01$), and there was a trend for decreased FFA with the meal in pair-fed mice ($P = .06$, Fig. 2A). In the *ob/ob* mice, there was only a decrease in plasma FFA in the leptin-treated group ($P = .006$, Fig. 2B). There was no significant change in FFA after feeding in the saline or pair-fed *ob/ob* mice (Fig. 2B).

The effect of 2 weeks of leptin administration on plasma glucose before and after the meal is shown in Fig. 3. In the WT animals, there was an increase in glucose after the meal in the leptin-treated ($P = .007$) and pair-fed mice ($P = .026$, Fig. 3A), but not in saline-treated mice. In the *ob/ob* animals, there was an increase in plasma glucose after the meal in all mice (Fig. 3B).

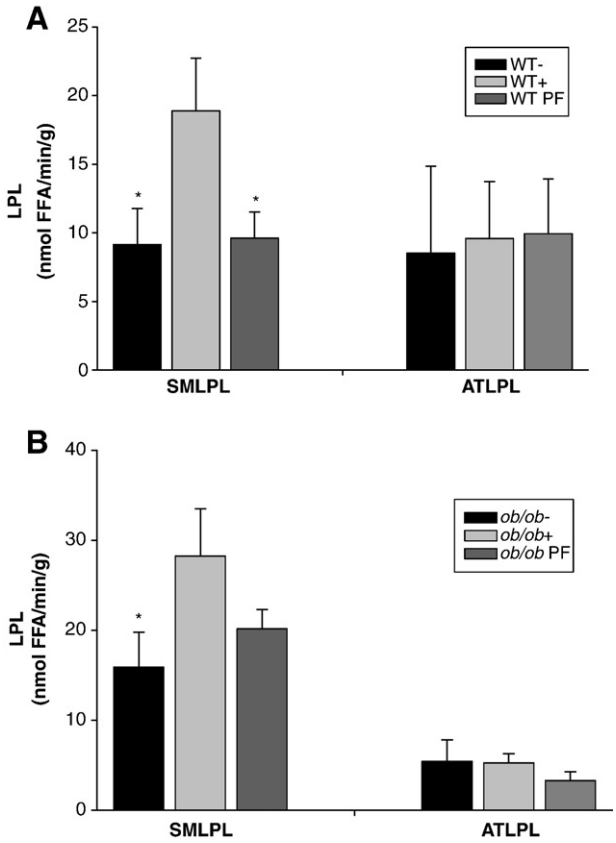

Fig. 1. A, Effect of leptin administration on LPL activity in WT mice. B, Effect of leptin administration on LPL activity in *ob/ob* mice. Values are mean ± SE. WT−, wild-type mice treated with saline; WT+, wild-type mice treated with leptin; WT PF, wild-type mice pair fed to WT+; *ob/ob*−, *ob/ob* mice treated with saline; *ob/ob*+, *ob/ob* mice treated with leptin; *ob/ob* PF, *ob/ob* mice pair fed to *ob/ob*+. *$P < .05$ vs SMLPL leptin.

The area under the TG excursion curve was used as a reflection of LPL-dependent TG-rich lipoprotein lipid metabolism in the postprandial state (Fig. 4). In the WT mice, there was no significant treatment effect on either the area under the TG excursion (AUC) or the integrated area under the TG excursion (IAUC) (Fig. 4A). In *ob/ob* mice, the TG excursion AUC was lower in the leptin-treated than

Table 1
Animal characteristics after 2 weeks +/− leptin

	WT−	WT+	WT PF	*ob/ob*−	*ob/ob*+	*ob/ob* PF
No. of animals	9	10	10	8	10	9
Age (wk)	11.6 ± 0.1	11.5 ± 0.1	11.3 ± 0.1	11.5 ± 0.1	11.6 ± 0.1	11.2 ± 0.1
Weight (g)*	198 ± 09	195 ± 08	191 ± 08	516 ± 09	438 ± 08	456 ± 08
FFA[a] (μmol/L)[†]	1049 ± 42	1087 ± 115	1226 ± 185	1713 ± 303	1187 ± 145	1977 ± 310
Glucose[a] (mg/dL)[‡]	233 ± 25	221 ± 11	281 ± 37	675 ± 87	436 ± 72	671 ± 52
TG (mg/dL)	92 ± 13	89 ± 78	88 ± 94	119 ± 32	137 ± 10	162 ± 23

[a] Final concentration.
* $P < .001$ *ob/ob* vs WT; $P < .001$ treatment (leptin vs pair fed vs WT).
[†] $P = .005$ *ob/ob* vs WT; $P = .066$ (leptin vs pair fed vs WT).
[‡] $P < .001$ *ob/ob* vs WT; $P = .009$ (leptin vs pair fed vs WT).

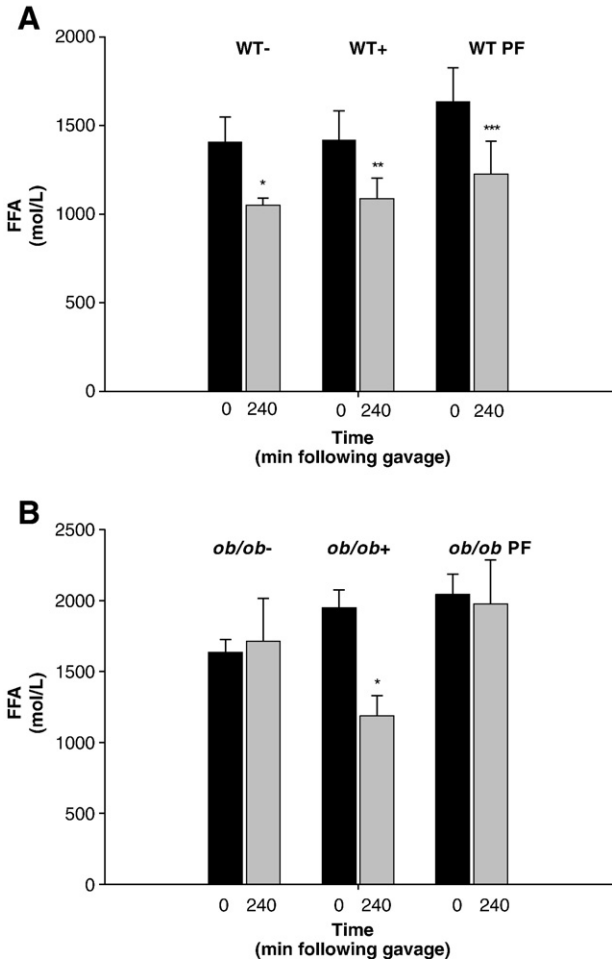

Fig. 2. A, Effect of leptin administration on FFA in WT mice. *P = .03, **P = .01, and ***P = .06 when comparing 0 vs 240 minutes. B, Effect of leptin administration on FFA in *ob/ob* mice. *P = .06 when comparing 0 vs 240 minutes. Values are mean ± SE.

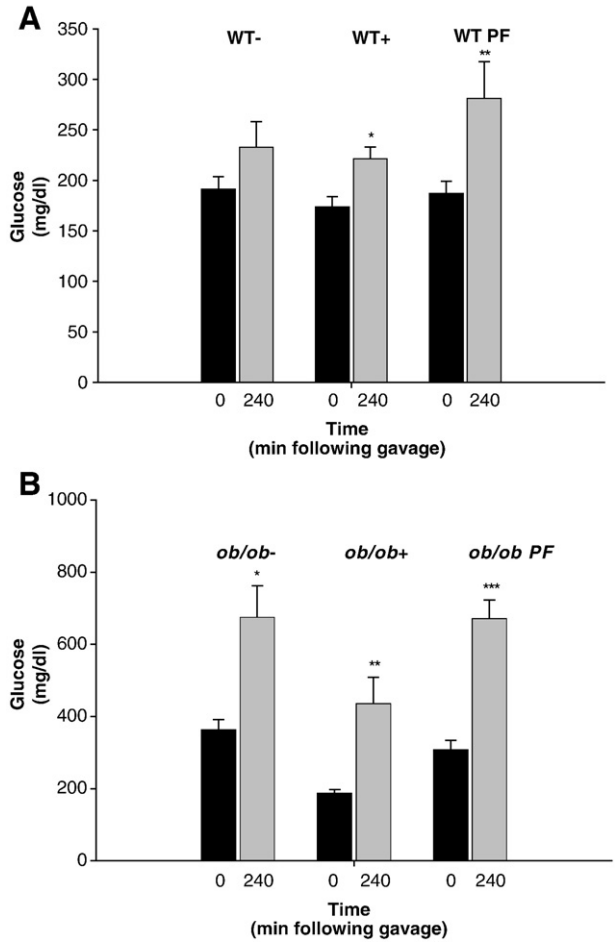

Fig. 3. A, Effect of leptin administration on glucose in WT mice. *P = .007 and **P = .026 when comparing 0 vs 240 minutes. B, Effect of leptin administration on glucose in *ob/ob* mice. *P = .001, **P = .009, and ***P < .001 when comparing 0 vs 240 minutes. Values are mean ± SE.

the pair-fed mice (P = .012); and the IAUC was also lower in the leptin-treated than the saline-treated mice (P = .027, Fig. 4B). Of interest, there was an inverse relationship between the TG IAUC and the level of SMLPL in leptin-treated WT mice, at r = −0.38 (P < .05).

4. Discussion

Two weeks of leptin treatment reduced weight in *ob/ob* but not in WT mice. However, leptin increased SMLPL in WT mice, with a lesser but borderline effect in *ob/ob* mice (P = .08, leptin vs WT). The inverse relationship between TG IAUC and SMLPL in WT mice suggests that leptin modifies lipid trafficking toward skeletal muscle where oxidation ensues. This concept is also supported by the observation that leptin failed to modify ATLPL, permitting a relative partitioning of TG-rich lipoprotein TG fatty acids to pathways of oxidation rather than storage. A similar effect was not apparent in *ob/ob* mice.

This is the first study to examine the effect of leptin on LPL activity in the fed state; however, some studies have addressed the effects of leptin on LPL under alternative conditions. Ranganathan et al [12] failed to show an effect of 24 hours of leptin treatment on basal or insulin-stimulated LPL activity in cultured rat adipocytes. Similar results were observed in *ob/ob* adipocytes. Lopez-Soriano et al [13] measured ATLPL and SMLPL in ad libitum–fed Wistar rats 3.5 hours after a single intravenous injection of 1 mg/kg leptin (PeproTech, Rocky Hill, NJ). When compared with WT rats, no effect of leptin on SMLPL or ATLPL was seen. In another experiment, increases in ATLPL messenger RNA were seen in mice treated with leptin (20 mg/[kg d]) for up to 14 days; however, there were no measurements of ATLPL activity in this study [14]. From a substantial volume of ATLPL literature, one cannot assume that changes in ATLPL gene expression are accompanied by changes in ATLPL activity [6,15].

Free fatty acids and glucose at 240 minutes after the fat bolus (gavage) were not consistently or significantly altered by leptin; however, in *ob/ob* mice, leptin lowered levels of

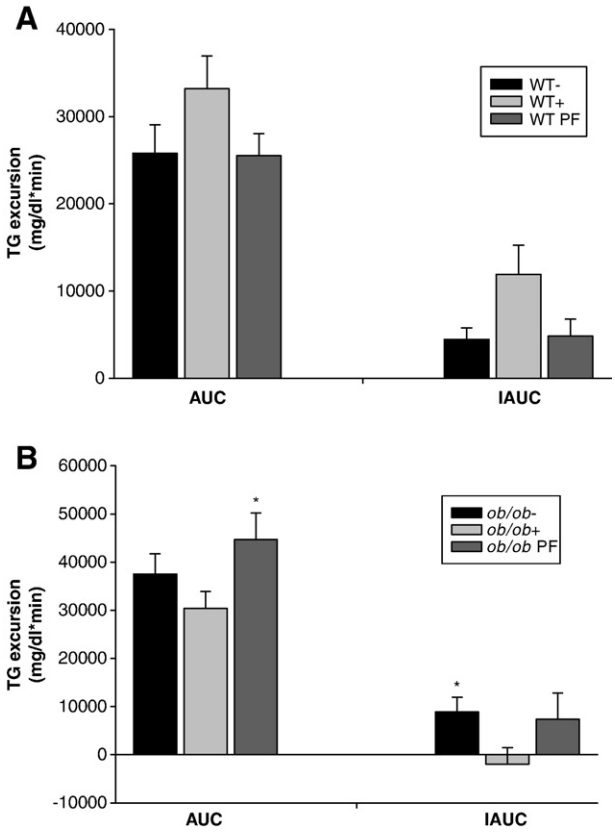

Fig. 4. A, Effect of leptin administration on TG excursion in WT mice. B, Effect of leptin administration on TG excursion in *ob/ob* mice Values are mean ± SE. *$P < .05$ vs leptin.

FFA after the meal, an effect not demonstrated in saline-treated or pair-fed *ob/ob* mice. Moreover, in *ob/ob* mice, leptin tended to reduce the postmeal increase in glucose compared with that seen in saline-treated and pair-fed *ob/ob* mice. In addition, in comparison to the response seen in pair-fed *ob/ob* mice, leptin reduced the incremental area of the postmeal TG excursion. Although some of this effect was probably related to the postmeal reduction in FFA, with reduced substrate for very low-density lipoprotein TG synthesis and secretion [16,17], there was a relationship between the TG IAUC and SMLPL.

The importance of SMLPL in controlling plasma TG-rich lipoprotein metabolism in mice is supported by several lines of evidence. When mice with overexpression of human LPL in skeletal muscle were crossed with hypertriglyceridemic apolipoprotein C-II transgenic mice, a dose-dependent reduction of plasma TGs was seen [18]. In addition, RXRλ-deficient mice have increases in SMLPL and lower fasting levels of plasma TGs [19]. In addition, SMLPL is particularly relevant to very low-density lipoprotein metabolism and is sufficient to compensate for the lack of LPL in other tissues [20].

The long-term administration of leptin results in depletion of body fat [2,3]. The mechanism behind this effect is incompletely understood, but appears not to be solely due to decreased energy intake alone, as pair-fed animals maintain more body fat than leptin-treated animals [21,22]. A number of studies have demonstrated that leptin administration increases muscle lipid oxidation and energy expenditure by both direct and indirect effects on skeletal muscle [23-26]. In addition to the effect of leptin on SMLPL, another mechanism of leptin action on postprandial TG-rich lipoprotein metabolism could be through increased clearance of lipoproteins by an interaction with the hepatic-lipolysis–stimulated receptor [27].

Several limitations exist for these experiments. First, there was a significant increase in leptin concentrations after injection and more so in *ob/ob* than WT mice. Although it is unclear if there were differences in leptin clearance between *ob/ob* and WT mice, the difference between the 2 groups is likely due to differences in dose (that was given on a per kilogram of total body weight basis) and volume of distribution. Second, the impacts of tissue-specific changes in LPL were not accompanied by measurements of lipid storage or oxidation.

In summary, 2 weeks of leptin administration variably increased SMLPL and favorably modified postprandial lipid metabolism in WT and *ob/ob* mice. Although the effect of leptin on LPL was specific to skeletal muscle and not adipose tissue, these data provide another example of reductions in leptin resistance after weight reduction.

Acknowledgment

Funding from Amgen (Thousand Oaks, CA) supported this work.

This study was approved by the University of Colorado Denver IACUC.

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