Effect of a five-week high-fat diet on serum-lipid composition and LPL mRNA expression in rat skeletal muscles

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(Received: 2013/05/13, Revised: 2013/06/23, Published online: 2013/06/27)

ABSTRACT

Our purpose was to investigate the effect of a 5-week high-fat diet on the body weight, blood components [triglycerides (TGs), free fatty acids (FFAs), and glucose], and lipoprotein lipase (LPL) mRNA expression in the skeletal muscles of rats. Body weight increased overtime in experimental and control groups without significant differences. In terms of the blood components, the density of TG was significantly lower in the high-fat diet group compared to the control, whereas FFA and glucose levels were similar in the two groups. Although the levels of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA expression were similar between the groups, LPL mRNA expression was significantly higher in the high-fat diet group than that in the control group. The results of this study suggest that a high-fat diet enhances LPL mRNA expression, as well as possibly increases fat metabolism. For a better understanding of the relationship between diet patterns and fat metabolism, further analysis of genes related to the fat metabolism is warranted.

Keywords: High-fat diet, LPL mRNA, skeletal muscle, rats

INTRODUCTION

The development of obesity has been associated with enzymes and receptors that control the basic mechanisms of skeletal muscle and adipose tissues. For instance, the excessive consumption of saturated fatty acids, induced by lipoprotein lipase (LPL), very low-density lipoprotein-receptor (VLDL-R), hormone-sensitive lipase, and carbohydrate intake are considered the main causes of obesity [19]. Researchers have reported that obesity is one of the risk factors for chronic diseases and induces various complications because of abnormal physiological changes in the body, and that the combination of exercise, diet, and the habits in daily life has considerable effects on the treatment of obesity [5,9,20].

LPL, an enzyme that hydrolyzes lipoproteins that consist of triglycerides and proteins for lipid metabolism, is an important factor in the prevention of high triglyceride-related atherosclerosis [7,8,13]. In terms of the mechanism of LPL, 95% of lipids in ingested food are stored as triglycerides,

which release high amounts of energy (~9 kcal) and are relatively large molecules that constitute solid fats. Triglycerides are hydrophobic and form lipoproteins that are transported to peripheral tissues through circulation. Based on the composition rates of apoproteins, triglycerides, cholesterol, phospholipids, and receptors, lipoproteins are classified into chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoprotein (HDLs) [3]. These 4 kinds of lipoproteins play different roles in various locations depending on the apoprotein composition. For example, chylomicrons are generated in the small intestines, and VLDLs are synthesized in the liver, decomposed by LPL, and transported to peripheral tissues [3]. The interior portion of lipoproteins contains hydrophobic triglycerides and cholesterol esters, whereas the exterior lipoproteins possess both hydrophilic and hydrophobic micelles, forming into cholesterol, phospholipids, and apolipoproteins that circulate through the blood. Fatty acids are mainly transported to

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muscles and adipose tissues, resynthesized into triglycerides, and glycerol is metabolized predominantly in the liver [3]. Lipid transport pathways include processes that LPL hydrolyzes lipoproteins through the substrate-enzyme interaction of LPL and apoCII in the cytomicro extrinsic pathway, which contains a large amount of triglycerides, and the VLDL intrinsic pathway [14].

According to Szalowska *et al.* [23], LPL is formed in adipose tissues, heart, skeletal muscle, and various cell tissues. It has been reported that 100% of LPL is synthesized in adipose tissues, 86% in the heart, 26% in the lungs, 15% of liver and less than 7% in other organs, with minimal expression in the spleen, ovary, and adrenal glands [2].

A number of studies have investigated the relationship between high-fat diet consumption and LPL activity. A study reported that reduced insulin resistance and high levels of glucose transport were observed in high-fat diet supplemented with n-3 polyunsaturated fatty acids compared to a high-fat diet group, which were associated with difficulties in glucose transport due to a reduced glucose level [6]. In another study, when obese rats were subjected to a high-fat diet for 7 weeks, increased LPL concentration in adipocytes was observed, and in albino rats fed on a normal diet (AIN 93) and those fed on a high-fat and high-cholesterol diet, elevated LPL activity in the epididymal adipose tissues and mesenteric adipose tissues was observed [12].

Brown & Layman [3] reported that LPL activity varied depending on the composition of saturated fatty acids, unsaturated fatty acids, high-carbohydrate diet, and high-protein diet, as well as on the skeletal muscle, blood, and cardiomyocytes. By comparing LPL activity in an 8-week high-fat diet group, they observed a significant increase in the heart, followed by the soleus muscle and adipose tissues. Significantly low activity was also seen in the gastrocnemius muscle.

In another study using rats fed on a 2-h high-fat, high-carbohydrate, or normal diet, LPL activity was significantly elevated in the normal and high-fat diet groups, and in white adipose tissues of the high-carbohydrate group. Although no significant intergroup differences in LPL activity was observed in the muscle, the high-fat diet showed a significantly high value in the heart muscle. LPL activity was relatively lower in the gastrocnemius, soleus, and heart muscles compared to brown adipose tissues [21].

A study on LPL activity under an exercise plus diet condition in albino rats resulted in an increased Apo-C II level and LPL activity and decreased VLDL-C level when fed on ginseng saponin and subjected to swimming [15]. Park *et al.* [16] reported that 12 weeks of aerobic exercise resulted in

a significant elevation of serum LPL in obese elderly women and this increase in LPL activity was required for the transport of lipids stored in the body to the serum for fat metabolism. Similarly, it has been reported that exercise significantly increased LPL activity, and the LPL action significantly reduced triglycerides and increased HDL-C [10]. In terms of expression of genes associated with a high-fat diet, the expression of UCP3 and HMG-CoA reductase messenger RNA (mRNA), which are related to lipid metabolism, has been reported to increase over time [11].

Despite the extensive research on the effects of diet and exercise on LPL activity, studies investigating changes in LPL mRNA expression in skeletal muscles due to the intake of a high-fat diet are limited. Therefore, the objective of this study was to evaluate the effects of a high-fat diet on blood components triglycerides (TGs), free fatty acids (FFAs), and glucose) and on the LPL mRNA expression in skeletal muscles.

MATERIALS AND METHODS

Experimental animals and diets

In total, 20 5-week-old male Sprague Dawley rats (Orient Bio Inc., Korea) were utilized in this study. The rats were acclimatized for one week for stress relief and pre-feeding purposes. The animals were then randomly divided into the control group (CON) and the high-fat group (HF) ($n = 10$ each). During acclimatization, commercially available rat diet (5L79, Orient, Korea) and drinking water were provided *ad libitum*.

After acclimatization, the CON group was fed on an AIN-76 Basic Diet and the HF group on a high-fat diet (Dyets, USA) containing 40% (w/w) beef tallow, which was based on the AIN-76 Basic Diet. To measure daily diet intake, the weight of the diet container was determined before adding the feed, and the weight of the container with the feed for 24 h (50–60 g) was then measured. On the following day, around the same time, the weight of the feed left uneaten, together with the container, was weighed, recorded, and the difference calculated from these measurements were treated as the daily diet intake.

Diet intake and body weight were measured around 08:30 to 09:30 every morning using an electronic balance (IB-6100 balance, Innotem, Japan). The study was performed in a sterile laboratory (SP1 level: sterile clothing) and rearing room of the research center at Konkuk University. The dark cycle was controlled every 12 h, in which 08:00–20:00 constituted the light period and 20:00 to 08:00 the dark period, maintaining at $23 \pm 2^\circ\text{C}$ room temperature, and 50% relative humidity.

Table 1. Composition and energy content of the experimental diets

Ingredient	Amount (g/kg)	
	CON	HF
Casein	200	200
DL-Methionine	3	3
Cornstarch	150	150
Sucrose	500	150
Cellulose	50	50
Mineral Mix	35	35
Vitamin Mix	10	10
Choline Bitartrate	2	2
Maltose Dextrin	-	-
Corn Oil	50	-
Beef Tallow	-	400
grams/kg	1000.0	1000.0
Kcal/g	3.79	5.54

Table 2. Feed composition and intake of experimental rats

Group	CON	HF
Number	10	10
Intake	AIN-76 Basic Diet	AIN-76 Basic Diet + 40% Beef tallow
Quantity (Total g/5 wk)	691.425 (1 g = 3.79 Kcal)	499.983 (1 g = 5.541 Kcal)
Quantity (Total kcal/5 wk)	2621	2770
Period (weeks)	5	5

Sterile bark in the cages was replaced once a week, and the diet composition is presented in Table 1.

Blood analysis

Rats were anesthetized through intraperitoneal injection of Zoletyl (40 mg/kg) and Lumpen (5 mg/kg) and then approximately 10 mL of venous blood was collected in a tube containing EDTA through abdominal aspiration. The collected blood was centrifuged at 3,000 rpm for 10 min at 4°C and the isolated plasma was immediately stored at -80°C until further analysis. Plasma TGs were extracted using TG reagents (Siemens, USA) kit and then the concentration was measured using a spectrophotometer (Advia, USA). Plasma glucose and FFAs were extracted using a glucose hexokinase (Siemens, USA) kit and NEFA HR.II (Wako, Japan) kit, respectively, and then the concentrations were determined using a spectrophotometer (Hitachi, Japan).

Skeletal muscle removal and RNA quantification

On the last day of the 5-week diet, the rats were fasted

Fig. 1. Agarose electrophoresis of extracted RNA**Table 3.** Primer sequences used in this study

Gene	Primer sequence	
LPL	Sense	5'-TCACCAGCATCCCCATTATT-3'
	Anti-Sense	5'-ATAGCCACAACAGCGTTTCC-3'
GAPDH	Sense	5'-GCCCAGCAAGGATACTGAGA-3'
	Anti-Sense	5'-GGGTGCAGCGAACTTTATTG-3'

for 3 h and induced to general anesthesia by intraperitoneal injection of Zoletyl (40 mg/kg) and Lumpen (5 mg/kg). Through abdominal injection, 10mL of venous blood was collected in a tube containing EDTA. For skeletal muscles, the soleus muscle was collected in the experimental rats and stored at -80°C until further analysis.

To extract total RNA from the collected skeletal muscles, 1 mL of the TRI reagent (Sigma-Aldrich, Inc., USA) was added to 50-100 mg of muscle tissues and homogenized on ice for 2 min using a homogenizer (PRO Scientific Inc., USA), collecting approximately 50 mL of total RNA.

The purity of the extracted total RNA was determined at 260 and 280 nm using a UV spectrophotometer (UV-mini 1240, Shimadzu Co., Japan). Approximately 2 mL of total RNA was subjected to gel electrophoresis using a 1% agarose gel and isolated rRNA 18S and rRNA 28S bands were utilized in real-time PCR analysis (Fig. 1).

Analysis of mRNA expression using real-time PCR

Primers were generated using Primer 3 version 0.4 (Web software provided by Steve Rozen and Whitehead Institute for Biomedical Research) and sense and anti-sense primers were created for the upstream open reading frame (URF) regions of the sequences (Table 3).

Expression of the quantified RNA was determined by iQ5 Multicolor Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., USA) at 30 ng/2μL of RNA using One-Step SYBR RT-PCR kit (TaKaRa, JAPAN).

Data processing

The SPSS 18.0 Package was utilized to calculate for the

means and standard deviations. Changes in body weight in terms of the group (2) $\times$ measurement time (6) after the 5-week diet were analyzed by two-way repeated ANOVA. Additionally, independent sample t-test was conducted to compare blood components and LPL mRNA expression between the two groups (i.e., CON and HF groups). A p-value less than 0.05 was considered as statistically significant.

RESULTS

Changes in body weight

Table 4 shows the changes in body weight observed during the 5-week high-fat diet.

With respect to the changes in body weight by group and measurement time, as described in Table 4, no significant differences were observed between the groups, where as differences were observed across the various time points [$F(5,75) = 3101.019$, $p < .001$]. In addition, the interaction between the groups and the time points [$F(5,75) = 5.502$, $p < .001$] was significant. In a post-hoc test for interaction, no significant differences between groups at each time point was observed, although all groups showed significant differences at each time point by group.

Blood components

Table 5 lists the blood components of two groups that were subjected to a 5-week high-fat diet.

As shown in Table 5, plasma TG concentrations were significantly low in the HF group compared to that of the CON ($p < .05$). No significant intergroup differences in plasma FFA and glucose levels were observed.

LPL mRNA expression

No differences in the GAPDH and LPL/GAPDH mRNA expression levels were observed between two groups. LPL mRNA expression, on the other hand, was significantly higher in the HF group compared to that of the CON group ($p < .001$).

Table 5. The changes in plasma TG, FFA, and glucose levels in each group

Group	TG(mg/dL)	FFA(μ Eq/L)	Glucose(mg/dL)
CON	145.00 $\pm$ 21.51	327.70 $\pm$ 137.38	238.90 $\pm$ 43.80
HF	115.25 $\pm$ 28.65*	357.33 $\pm$ 110.44	203.44 $\pm$ 34.37
t-Values	2.440 [#]	-.514	1.947

Values are Means $\pm$ SD CON; control Group, HF; High fat diet group

* $p < .05$ Significant difference from CON

Table 6. Expression of GAPDH, LPL, and LPL/GAPDH

	GAPDH(ng)	LPL(ng)	LPL/GAPDH(%)
CON	0.454 $\pm$ 0.142	0.330 $\pm$ 0.118	1.368 $\pm$ 0.827
HF	0.414 $\pm$ 0.159	0.755 $\pm$.219***	2.267 $\pm$ 0.883
t-Values	.493	-5.189 ^{###}	-2.010

Values are Means $\pm$ SD CON; control Group, HF; High fat diet group

*** $p < .001$ Significant difference from Control

DISCUSSION

This study has exhibited that body weight increased in the HF and CON groups over time during a 5-week diet. However, no significant changes in body weight in the HF diet group were observed during the entire time course as compared to the CON group.

In this regard, we reviewed related previous studies: Picard *et al.* [17] reported that when 120 rats were fed divided into two groups and fed with either a normal diet (Chow G: regular animal diet) or a high-carbohydrate and high-fat diet (HSHF G: carbohydrate, 41%;fat, 39%;and protein, 20%), the body weight of the rats in both groups increased after 4 weeks and a significantly increased body weight was observed in the HSHF group compared to the normal diet group. Moreover, Yu *et al.* [26] conducted a study using 5-week-old mice for 30 days, divided into 4 groups of 8 mice each (CON HF, HF+ herbal acupuncture 150 mg, and HF+300 mg) and observed a significant elevation of body weight in all 4 groups after 30 days of diet compared to the baseline weight, with the HF group showing a significant increase compared to the CON group. In another study using 4-week-old male C57BL/6J rats fed on a low-fat, low-carbohydrate diet (LL: 3% fat 5% sucrose), high-fat diet (HF: 45% fat), and high carbohydrate diet (HS: 50% sucrose) for 55 weeks after 1 week of an adaptation period, the HF group showed a significant increase in the body weight compared to the LL and HS groups [22].

Table 4. The changes in body weight in each group (g)

	0 wk	1 wk	2 wk	3 wk	4 wk	5 wk
CON	172.85 $\pm$ 8.33	226.63 $\pm$ 14.09***	288.11 $\pm$ 16.71***	345.26 $\pm$ 18.57***	395.20 $\pm$ 24.78***	430.91 $\pm$ 30.12***
HF	172.58 $\pm$ 7.47	224.02 $\pm$ 11.59***	286.99 $\pm$ 17.03***	348.62 $\pm$ 19.94***	409.29 $\pm$ 20.98***	448.94 $\pm$ 22.15***

Values are Means $\pm$ SD CON; control Group, HF; High fat diet group

*** $p < .001$, Significant difference from 0 wk

These studies resulted in significantly elevated body weight in the HF diet group after the diet, which is not in agreement with the results obtained in our current study. Therefore, we searched for the reasons behind this discrepancy and this may have been attributable to the amount of food consumed by our experimental animals (Table 2). In terms of total diet intake for 5 weeks, the HF diet group consumed a smaller amount of food, 499.988 g, compared to the CON group, 691.425 g, which may be converted to 2,770 Kcal and 2621 Kcal, respectively, based on its dietary composition. Therefore, even though there was a difference in the quantities of food consumed between the two groups, the total calorie intake between the two groups was very similar, indicating that significant differences in weight may not be observed.

The present study observed that after a 5-week diet, the TG level of the animals in the HF group was significantly lower compared with that of the CON group ($p < .05$). In a previous study, 3 groups of rats were fed with 3 different diets, namely a normal diet, high-carbohydrate diet, and a high-fat diet, for 4 weeks and sacrificed by hour after being subjected to fasting for 24 h to measure the plasma TG level. It was significantly higher after 3 h in the high-carbohydrate and the high-fat diet groups compared to the normal diet group [17]. Another study also observed significantly increased plasma TG level in the high-fat diet group than the control group after 30 days of the study using 5-week-old mice [26]. In addition, when 4-week-old C57BL/6J rats were divided into the high-fat diet group, the high-carbohydrate diet group, and low-carbohydrate/low-fat diet group, the plasma TG concentration after 55 weeks was significantly higher in the high-fat diet group compared with the other groups [22].

According to the study by Applegate *et al.* [1], on the other hand, when 5-week-old rats were divided into the control group (Control; CON = 43 rats; hydrated glucose, 59.8%) and the high-fat diet group (High Fat; HF = 48 rats; hydrogenated vegetable shortening, 37%), no intergroup differences in TGs were observed at week 15, whereas significantly low TGs were observed in the high-fat diet group compared to the control group after 21 weeks. This result was in agreement with the present study in that the high-fat diet group showed significantly low plasma TGs compared to the control group after 5 weeks. Similarly, a study in which SD rats were fed on a high-fat diet (HF) (protein: 22.3%; carbohydrate: 8.40%; fat: 62.67%) and the high-sucrose diet (HS) (protein: 9.95%; carbohydrate: 81.39% (in 60% sucrose); fat: 4.80%) for 2 weeks showed significantly low TG concentrations in the high-fat diet group compared to the high-sucrose diet group [24]. Meanwhile, a human study, in which 43 healthy male participants were randomly divided into the high-fat diet

group (38% carbohydrate, 46%-18% saturated fat, 12% unsaturated fat) and the low-fat diet group (60% carbohydrate, 24% total fat-6% saturated fat, 4% unsaturated fat) and fed for 6 weeks, reported that TG concentration was significantly elevated in the low-fat diet group compared to the high-fat diet group [4].

We observed significantly higher triglyceride levels in the CON group compared to the HF diet group, and this is in agreement with a study conducted by Kusunoki *et al.* (2005), which reported that activated LPL in skeletal muscle reduces TGs and increases HDL-C.

In addition to the fat absorption and decomposition mechanisms, it is considered attributable to the triglyceride synthesis by glucose metabolism. Acetyl-CoA utilized in fatty acid synthesis is obtained in glucogenesis, partially in carbon skeletal decomposition of amino acids and fatty acid oxidation. In particular, excessive intake of carbohydrates elevates NADPH, thus increasing fatty acid synthesis.

In this study, we investigated the LPL mRNA expression in skeletal muscle after 5 weeks of diet given to the HF diet group and the CON group. The GAPDH mRNA expression did not indicate significant intergroup differences, whereas the LPL mRNA expression was significantly higher in the HF group than in the CON group ($p < .001$). Moreover, the LPL/GAPDH mRNA tended to be higher in the HF group than in the CON group, although without any significant intergroup differences.

Lee *et al.* [12] reported that LPL activity significantly increased in visceral adipocytes and epididymal adipocytes of the high-fat cholesterol diet group, especially in the epididymal adipocytes rather than in the visceral adipocytes in an experiment with 5-week-old SD rats, in which they were divided into the normal diet group and the high-fat cholesterol diet group and fed for 4 weeks after a week of pre-adaptation. Even if the results were not obtained from skeletal muscle, they are consistent with the results of the present study. Moreover, in a study analyzing LPL activity in skeletal muscle after the knockout of skeletal muscle LPL in rats, the highest LPL activity was observed in the heart, followed by white adipose tissues, red muscle in skeletal muscle, and white muscle in skeletal muscle [24].

Brown & Layman [3] reported that LPL activity was significantly higher in the soleus muscle of the high-fat diet group than that in the control group in SD rats because of an 8-week high-fat diet. In another study, when P14C76L10 (high carbohydrate, low fat, normal protein), P53C35L10 (normal carbohydrate, low fat, high protein), and P55L45 (carbohydrate free, high fat, high protein) were administered to 24 Wistar rats for 42 days, LPL activity tended to be

slightly higher in P55L45 [18]. Moreover, significantly higher LPL activity was observed in the high-fat diet group when SD rats were fed with high-carbohydrate diet and the high-fat diet for 2 weeks [25].

Taken together, although it is generally known that body weight increases in the HF diet group compared to the CON group, we did not observe any significant intergroup differences in body weight under similar total calorie intake. It was also confirmed that HF diet enhances the LPL mRNA expression. However, a study sequel will have to be conducted to draw a clear conclusion regarding the low TG level shown in this study.

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