Effect of dietary macronutrient composition on tissue-specific lipoprotein lipase activity and insulin action in normal-weight subjects

Trudy J Yost, Dalan R Jensen, Bryan R Haugen, and Robert H Eckel

ABSTRACT The effects of macronutrient composition on fasting and postprandial activities of adipose tissue lipoprotein lipase (ATLPL) and skeletal muscle LPL (SMLPL) and on insulin sensitivity (SI) were studied in 25 normal-weight subjects. Each subject was fed a high-carbohydrate (HC) diet for 16 d and a high-fat (HF) diet for 16 d, in randomized order. On day 15 of each diet, biopsies for ATLPL and SMLPL were done in the fasted state and 6 h postprandially. On day 16 of each diet, a euglycemic clamp was used to measure SI. There was no effect of diet composition on fasting ATLPL or SMLPL. With both diets and in both tissues, LPL increased significantly from fasting to 6 h postprandially. In adipose tissue only there was a significant difference between the 2 diets in LPL meal response (HC > HF, P = 0.024). There was no effect of diet composition on SI. After the HC diet only, there were significant correlations between fasting SMLPL and SI, but not ATLPL. After the HF diet, associations between insulin action and LPL were evident only in the postprandial state. In summary, 16 d of HC compared with HF feeding in normal-weight subjects increased the responsiveness of ATLPL to an HC compared with an HF meal. However, the same diets had no effect on fasting ATLPL or SMLPL, the responsiveness of SMLPL to a meal, or SI. These data suggest that in normal-weight subjects habitual dietary carbohydrate intake may have a stronger effect on subcutaneous fat storage than does dietary fat intake.

KEY WORDS Macronutrient, lipoprotein lipase, insulin action, adipose tissue, skeletal muscle, high-carbohydrate diet, high-fat diet, diet composition

INTRODUCTION

The macronutrient content of the human diet affects lipoprotein lipase (LPL) activity (1, 2) and most often these effects are tissue specific. In humans, when adipose tissue LPL (ATLPL) is measured after an overnight fast, diets high in carbohydrate are usually associated with increases in ATLPL (3, 4) but with no changes or decreases in skeletal muscle LPL (SMLPL) (4). The effect of high-fat diets on tissue-specific regulation of LPL in humans has not been tested. Overall, these relations may be explained by diet-dependent changes in insulin secretion, insulin sensitivity (SI), or both. We showed previously in normal-weight subjects that insulin infusion, under conditions of euglycemia, has a stimulatory effect on ATLPL (5, 6) but an inhibitory effect on SMLPL (6, 7). Moreover, the ingestion of fat has been shown to markedly blunt the insulin- and glucose-stimulated response of LPL in adipose tissue (8).

Several studies in humans have shown that the macronutrient content of the diet can also alter insulin action (9–12). Some studies have shown that isoenergetic diets containing a higher percentage of energy as fat produce insulin resistance (9, 12), whereas other studies found no difference in SI after high-fat compared with high-carbohydrate feeding (13, 14). If an increased percentage of energy consumed as fat is truly associated with insulin resistance, that behavior may have long-term adverse consequences, specifically, the development of type 2 diabetes, dyslipidemia, and hypertension and increased risk of atherosclerotic cardiovascular disease (9, 12, 15). Although high-fat diets also appear to lead to obesity (16), insulin resistance may well be a better predictor of weight stabilization than of weight gain (17).

The purpose of this study was to determine the effect of dietary macronutrient composition on fasting ATLPL and SMLPL activities and on postprandial enzyme changes after a single meal. The relation between dietary induced changes in SI and tissue-specific LPL response was also examined.

SUBJECTS AND METHODS

Subject procedures

After approval of the protocol by the Colorado Multiple Institutional Review Board and the Scientific Advisory Committee of the Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Health Sciences Center, Denver.

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the General Clinical Research Center at the University of Colorado Health Sciences Center, 25 normal-weight individuals (15 men, 10 women) gave their informed consent and were enrolled in the study. Subjects were between 25 and 34 y of age (\(\bar{x} \pm \text{SEM}: 29 \pm 1\) y), were at their maximum body mass index (22.1 \(\pm 0.3\), in kg/m\(^2\)), and had been weight stable for 33 mo before enrollment. Each potential subject was given the Diet Habit Survey (18) to determine his or her current free-living diet composition.

Results of screening laboratory tests, including liver and renal panels, complete blood count, urinalysis, and measurement of serum electrolytes, fasting glucose, and thyroid-stimulating hormone, were within normal limits for each individual. Fasting lipid concentrations, including concentrations of triacylglycerol, cholesterol, HDL cholesterol, and LDL cholesterol, were also within the normal range. None of the subjects were taking medication that affected lipid or carbohydrate metabolism.

On day 0 of the study protocol, each subject was admitted to the General Clinical Research Center for fasting measurements of serum glucose and insulin concentrations and plasma triacylglycerol, total cholesterol, HDL-cholesterol, and LDL cholesterol, and were also studied to test whether changes seen in ATGL in the larger cohort were due to the diet or the meal. The mean age for these subjects was 30 \(\pm 3\) y and their mean body mass index was stable at 22.8 \(\pm 0.8\). Each of the 8 subjects was fed a single meal of either HC or HF composition (in randomized order) on 2 separate days, a minimum of 1 wk apart. Gluteral ATGL was measured in the fasted state and again 6 h postprandially and the meal-induced change in ATGL calculated.

Independent assessment of meal effect

An additional 8 normal-weight subjects (5 men, 3 women) were also studied to test whether changes seen in ATGL in the larger cohort were due to the diet or the meal. The mean age for these subjects was 30 \(\pm 3\) y and their mean body mass index was stable at 22.8 \(\pm 0.8\). Each of the 8 subjects was fed a single meal of either HC or HF composition (in randomized order) on 2 separate days, a minimum of 1 wk apart. Gluteral ATGL was measured in the fasted state and again 6 h postprandially and the meal-induced change in ATGL calculated.

Laboratory procedures

LPL activity was measured in 40–45-mg pieces of tissue as described previously (21). Heparin-releasable lipase activity was measured against an emulsified serum-containing \(^{14}\text{C}\)triolein substrate. Adipocyte size was determined by the method of DiGirolamo et al (22) after cells were isolated from tissue pieces in 2 g collagenase/L by the method of Rodbell (23).

Serum insulin concentrations were measured by radioimmunoassay (24). Serum fatty acid concentrations were measured enzymatically, with a colorimetric endpoint (25). Plasma triacylglycerol concentrations were measured enzymatically (26), as were serum glycerol concentrations (27). HDL cholesterol was separated from total cholesterol by use of the two-step dextran sulfate–magnesium chloride precipitation method of Warnick et al (28).

Data analysis

Variables of normal distribution were analyzed by using Student’s \(t\) test and Pearson correlation analyses (\(r\)). Variables that were not normally distributed were analyzed by using the Wilcoxon rank-sum test and Spearman rank analysis (\(r_s\)). Analysis of covariance was used to compare the results of the preprandial serum and plasma measurements on day 15, ie, concentrations of glucose, insulin, triacylglycerol, cholesterol, HDL cholesterol, and HDL\(_2\) cholesterol. Incremental area under the curve (IAUC) was calculated from the postprandial concentrations of glucose, insulin, triacylglycerol, fatty acids, and glycerol and was used as a summarizing measurement for each variable as described by Wolever and Jenkins (29). Analyses that yielded probabilities \(\leq 0.05\) were considered to be statistically significant. Results are presented as means \(\pm\) SEMs.

RESULTS

The study group of 25 normal-weight subjects consisted of 10 women and 15 men between 25 and 34 y of age (\(\bar{x} \pm \text{SEM}: 29 \pm 1\) y). At the screening visit, while the subjects were consuming a
free-living diet, the percentage dietary fat intake for the group was estimated to be 28 ± 1% with use of the Diet Habit Survey (18). The weight to be maintained for the women was 57.4 ± 1.7 kg and for the men was 76.7 ± 2.4 kg. The maintenance body mass index by sex was 20.5 ± 0.5 for women and 22.8 ± 0.6 for men. Weight stability was achieved over each diet phase (phase 1: women, 57.8 ± 1.6 kg, men, 77.1 ± 2.3 kg; phase 2: women, 58.2 ± 1.6 kg, men, 77.8 ± 2.3 kg).

There were no differences in any of the blood values measured in the fasted state on day 0 of each phase (Table 1). As expected, concentrations of HDL cholesterol were higher in women than in men (1.50 ± 0.10 compared with 1.09 ± 0.05 mmol/L, respectively, \( P < 0.001 \)), as were concentrations of HDL₂ cholesterol (0.34 ± 0.08 compared with 0.10 ± 0.03 mmol/L, respectively, \( P = 0.001 \)). The daily energy intake required for weight stability was not significantly affected by macronutrient composition (HC compared with HF: 16 129 ± 16 050 kJ/d; women consuming the HC compared with the HF diet: 16 610 ± 17 629 kJ/d). However, the daily energy intake was significantly lower with the HF diet, day 15 of both the HC and HF diets (Table 1) indicated that there were significant differences between the 2 meals for plasma glucose IAUC (HC < HF, \( P = 0.005 \)), serum insulin IAUC (HC < HF, \( P = 0.026 \)), and plasma triacylglycerol IAUC (HC < HF, \( P = 0.039 \)).

The LPL results of fasting blood analyses done on the morning of day 15 of both the HC and HF diets (Table 1) indicated that there was an effect of dietary macronutrient composition on fasting triacylglycerol (significantly lower with the HF diet, \( P = 0.002 \)), fasting HDL cholesterol (significantly higher with the HF diet, \( P = 0.013 \)), and HDL₂ cholesterol (significantly higher with the HF diet, \( P = 0.035 \)). Shown in Table 2 is the response of plasma and serum variables to meals of both compositions as analyzed by determining IAUCs for the value of each variable measured hourly from 0 to 6 h after the meal. There were significant differences between the 2 meals for plasma glucose IAUC (HC > HF, \( P = 0.005 \)), serum insulin IAUC (HC > HF, \( P = 0.026 \)), and plasma triacylglycerol IAUC (HC > HF, \( P = 0.039 \)).

The LPL results from the adipose tissue biopsies performed on each subject on day 15 of each diet are shown in Figure 1. There was no effect of diet composition on fasting (0 h) SMLPL activity. After both diets, SMLPL activity increased significantly from fasting to 6 h postprandially (HC: from 0.8 ± 0.4 nmol fatty acids · min⁻¹ · g⁻¹, \( P = 0.015 \); HF: from 0.8 ± 0.3 to 1.5 ± 0.2 nmol fatty acids · min⁻¹ · g⁻¹, \( P = 0.0001 \)). However, the 0–6-h change in skeletal muscle LPL activity was not significantly different between the 2 diets.

To test whether the relations of the aforementioned metabolic variables with ATLPL after HC and HF feeding were due to the diet or the meal, gluteal ATLPL was measured in 8 subjects in the fasted state (under free-living diet conditions) and then 6 h postprandially and the meal-induced change in ATLPL calculated. The results shown in Figure 2 indicate that there was no difference in the 0–6-h ATLPL meal response after the HC meal compared with after the HF meal (1.2 ± 0.5 compared with 1.5 ± 0.9 nmol fatty acids·min⁻¹·g⁻¹ cells, \( P = 0.27 \)). The 0–6-h ATLPL meal responses in these 8 subjects were similar to those in the 25 subjects. Therefore, the effects on LPL seen after 15 d of an HC compared with an HF diet in the present study of 25 subjects appear to have been due to the macronutrient composition of the diet rather than of the meal. The independent test group (8) also showed significant differences between the 2 meals in the calculated postprandial IAUC for...

**TABLE 1**

Fasting serum or plasma values of normal-weight subjects on day 0 and day 15 of a high-carbohydrate (HC) or high-fat (HF) diet

<table>
<thead>
<tr>
<th></th>
<th>HC diet</th>
<th>HF diet</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 15</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 0.1</td>
<td>4.6 ± 0.1</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>43 ± 7</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>1.13 ± 0.11</td>
<td>1.14 ± 0.11</td>
</tr>
<tr>
<td>Fatty acids (g/L)</td>
<td>—</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>Glycerol (g/L)</td>
<td>—</td>
<td>8.93 ± 0.83</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>3.98 ± 0.16</td>
<td>3.90 ± 0.16</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.27 ± 0.08</td>
<td>1.22 ± 0.06</td>
</tr>
<tr>
<td>HDL₂ cholesterol (mmol/L)</td>
<td>0.23 ± 0.05</td>
<td>0.19 ± 0.04</td>
</tr>
</tbody>
</table>

¹ x ± SEM; \( n = 25 \). Study design was as follows: diet phase 1 for 16 d (either HC or HF diet), followed by 4–6-wk washout, followed by diet phase 2 for 16 d (either HC or HF diet).

²,³ Significantly different from day 15 of HC diet: ² \( P < 0.01 \), ³ \( P < 0.05 \).

**TABLE 2**

Incremental areas under the curve (IAUCs) for normal-weight subjects on day 15 of a high-carbohydrate (HC) or high-fat (HF) diet

<table>
<thead>
<tr>
<th></th>
<th>HC Diet</th>
<th>HF Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose IAUC (mmol·h/L)</td>
<td>35 711 ± 755</td>
<td>34 226 ± 867²</td>
</tr>
<tr>
<td>Insulin IAUC (pmol·h/L)</td>
<td>12 185 ± 1459</td>
<td>9 056 ± 952³</td>
</tr>
<tr>
<td>Triacylglycerol IAUC (mmol·h/L)</td>
<td>52 438 ± 4039</td>
<td>52 736 ± 5082⁴</td>
</tr>
<tr>
<td>Fatty acid IAUC (g·h/L)</td>
<td>94 067 ± 6252</td>
<td>144 660 ± 7232</td>
</tr>
<tr>
<td>Glycerol IAUC (g·h/L)</td>
<td>28 042 ± 1605</td>
<td>36 318 ± 2723</td>
</tr>
</tbody>
</table>

¹ x ± SEM; \( n = 25 \).

²,³ Significantly different from HC diet: ² \( P < 0.01 \), ³ \( P < 0.05 \).
There was a significant increase in the 0–6-h meal response of SMLPL after the HC compared with the HF diets and meals were variable. Activity levels of SMLPL were seemingly affected by relative position on steady state insulin concentrations (HC compared with HF: 369 ± 21 compared with 371 ± 29 pmol/L) nor on steady state glucose concentrations (HC compared with HF: 4.4 ± 0.1 compared with 4.4 ± 0.1 mmol/L) achieved over the course of the euglycemic clamp. With the HC diet, the CVs for steady state insulin and steady state glucose were 28.4% and 7.3%, respectively. With the HF diet, the CV for steady state insulin was 38.9% and that for steady state glucose was 6.2%.

Overall, the tissue-specific changes in LPL activity after HC compared with HF diets and meals were variable. Activity levels of SMLPL were seemingly affected by relative Sf after 15–16 d of exposure to a diet high in carbohydrate. There was a significant inverse correlation between fasting serum insulin concentrations and the level of activity of SMLPL measured in the fasted state on day 15 with the HC diet (r = −0.433, P = 0.030). The relation between SMLPL activity and Sf after HF feeding was also shown by a positive correlation between fasting SMLPL activity and the GIR (r = 0.434, P = 0.030). These SMLPL correlations did not exist after HF feeding. Moreover, fasting ATPL activity was not correlated with either the fasting serum insulin concentration nor the GIR after HC feeding.

Although the above relations of fasting SMLPL activity with Sf were not evident after 15–16 d of the HF diet, there were several relations between metabolic variables that were unique to the HF macronutrient perturbation. The significant SMLPL correlations discovered under the HF feeding conditions, however, became evident only at the 6-h postprandial time point after the HF meal. On day 15, the response of SMLPL to the HF meal was inversely correlated with fasting serum glucose (r = −0.440, P = 0.028). Also, after the HF diet and HF meal, the 0–6-h change in SMLPL activity was positively correlated with Sf as measured by the GIR during the clamp study (r = 0.438, P = 0.028). In adipose tissue, a strong inverse correlation was found between the response of ATPL to the HF meal and fasting glucose the morning of day 15 (r = −0.630, P = 0.0007).
The HF meal than after the HC meal. However, an independent TLPL, but 6 h postprandially compared with fasting after both
25 normal-weight subjects also showed a significant increase in
activity increased on average 21% when measured 1 h
standard lunch (\(10 \text{ d}\) and then fed each a standard breakfast (isoenergetic diet (45% carbohydrate, 35% fat, and 20% protein) for
and Nikkila (35) had 14 moderately obese women consume an
insulin- and glucose-responsive enzyme under conditions of both
parenteral and oral energy stimulation (3, 5, 6, 33–36). Taskinen
and Nikkila (35) had 14 moderately obese women consume an
isoenergetic diet (45% carbohydrate, 35% fat, and 20% protein) for
10 d and then fed each a standard breakfast (\(3347 \text{ kJ}\)) and a
standard lunch (\(2092 \text{ kJ}\)) after a 10-h fast the night before. Gluteal
ATPL activity increased on average 21% when measured 1 h
after ingestion of the standard lunch. The data presented here in
25 normal-weight subjects also showed a significant increase in
ATPL, but 6 h postprandially compared with fasting after both
diets. The postprandial responsiveness of ATPL was lower after the
HF meal than after the HC meal. However, an independent examination of 8 normal-weight subjects who received HC and
HF meals only (without prior diet preparation) showed no effect of
the meal composition on the ATPL postprandial response. Therefore, the difference seen in the postprandial ATPL response to an HC meal compared with an HF meal in the present study was apparently dependent on the macronutrient composition of the preceding diet, rather than on the composition of the meal. As noted previously, there was no difference between the 2 diets in \(S_I\).

Skeletal muscle LPL activity is responsive to various physiologic changes, among them starvation and feeding. In humans, it has been shown that the consumption of higher quantities of carbohydrate results in lower SMLPL activity (4, 37). Lithell et al (4) had 7 normal-weight men take part in a study in which the diet was changed from an ordinary mixed diet to an HF diet (< 70% of energy) for 3 d, followed by an HC diet (> 70% of energy) for 3
fasting serum insulin concentrations were higher after the HC
diet than after the HF diet, as were serum triacylglycerol concentra-
tions. Fasting SMLPL activity, however, was lower after the
HC diet than after the HF exposure. The authors suggested that
the increased insulin concentration during the short-term HC diet
may have down-regulated SMLPL activity. It is important to note
that the diets in the study by Lithell et al were extreme in com-
position and given only for 3 d, the diet order was not random-
ized, nor was there a washout period between the 2 experimental
diets. A similar study done by Jacobs et al (37) showed similar
results but with the same study limitations.

The effects of more long-term dietary manipulation on fasting
SMLPL activity have been examined in humans. Kiens et al (38)
studied 19 physically trained men and found that 4 wk of an HF
diet (54% of energy) significantly increased (> 0.05) fasting
SMLPL activity compared with that when the individuals con-
sumed a “control” diet (< 43% of energy as fat). When dietary
macronutrient composition was then changed to 51% of energy
as carbohydrate for 4 wk, fasting SMLPL activity returned to
control levels and was again significantly less (< 0.05) than
after the HF feeding.

In contrast with the above studies, the data presented here
indicate that fasting SMLPL activity was unaffected by 15 d of
HC compared with HF feeding. Length of diet exposure was
much longer in the present study than in the studies by Lithell
et al (4) and Jacobs et al (37), and the 4–6-wk washout phase
between diets precluded any carryover effect of the previous
diet. Randomization of diet order and the less extreme macronu-
trient composition of the experimental diets are also factors that lend strength to the results presented here.

Several investigators have observed in in vivo studies in humans (6) and animals (39) that LPL activity often changes in
opposite directions (ATPL increases, SMLPL decreases) when
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insulin (40–42). In rats, HF diets have been shown to result in
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presented here for 25 normal-weight subjects, although SMLPL
response to a meal was not different between the 2 diets, SMLPL
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In the 25 normal-weight subjects studied, whole-body \(S_I\) was
variably affected by the macronutrient composition of the diet,
with the group data showing no significant effect. The variabil-
ity of \(S_I\) was expressed equally in both sexes. These results agree
with those reported by Borkman et al (14), who found that \(S_I\) was
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**FIGURE 3.** Mean glucose infusion rate (GIR, by individual) meas-
ured in 25 normal-weight subjects over the last hour of a 3-h insulin and
glucose infusion performed on day 16 of a high-carbohydrate (HC) diet
and on day 16 of a high-fat (HF) diet (in randomized order). Insulin was
infused at a rate of 258 pmol·min\(^{-1}·m^2\) with a variable infusion of 20%
dextrose to maintain the euglycemic goal. There was no significant
difference in the GIR between the HC and HF diets.

This relation was not seen in adipose tissue after the HC diet or
meal. In the smaller group of 8 subjects in whom there was no
prior diet preparation, no correlation was found between fasting
serum glucose and the 0–6-h postprandial change in ATPL after
either the HF or the HC meal.

**DISCUSSION**

Fasting ATPL activity has been shown to be similar in the
same individual when measured on separate occasions and
among individuals of the same body type (ie, lean or obese) (6,
8, 32). However, few studies have examined the effect of dietary
macronutrient manipulation on the fasting enzyme activity in
adipose tissue in humans. One study done by Pykalisto et al (3)
documented a 47% increase in fasting ATPL in obese control
subjects and obese subjects with type 2 diabetes after 2 wk of an
85%-carbohydrate diet compared with a control diet of normal
composition (45% carbohydrate). An 85%-carbohydrate diet,
however, is beyond the composition seen in the most extreme
nutritional intake patterns in the population. In the present study
of normal-weight, nondiabetic subjects in which both diets were
substantially altered but still realistic in composition, there was
no difference in fasting ATPL activity after 15 d of the HC
compared with the HF diet.

Many studies have supported the idea that ATPL is an
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ured after 3 wk of an HF diet. In fact, as seen in the data presented here, insulin-stimulated peripheral glucose uptake (measured during a euglycemic clamp) was the same with both diets in the study by Borkman et al. One difference in that study is that the 2 diets were fed consecutively with no washout phase separating them and a carryover effect was not assessed. Because both diets were artificially manipulated to include compositions beyond the normal range, it is hazardous to assume that there was no carryover effect. Swinburn et al (13) did a study in which 12 Caucasians and 12 Pima Indians (58.4–213.5 kg) were each fed an HC and an HF diet for 2 wk (randomized, crossover design). A frequent-sampling intravenous-glucose-tolerance test was carried out for determination of \( S_I \). No difference was found in \( S_I \) between the 2 diets, regardless of race, sex, or body weight (ie, obese compared with lean). Again, the administration of the 2 diets consecutively may have introduced a carryover effect.

As noted earlier, many investigators have shown that insulin action in humans can be altered by changes in the macronutrient content of the diet. In contrast with the results presented here, Lovejoy et al (9) found that \( S_I \) (measured with a frequent-sampling intravenous-glucose-tolerance test) was inversely correlated with percentage fat intake in 38 lean and obese subjects, suggesting that as individuals increased the proportion of fat in their diet, relative insulin resistance resulted. The results of the food-frequency questionnaire administered indicated that the habitual dietary composition of the lean subjects (\( n = 22 \)) was 36 ± 1% fat and 45 ± 1% carbohydrate, whereas that of the obese group was significantly different (42 ± 1% fat and 40 ± 1% carbohydrate, \( P < 0.01 \)). The data were not controlled for weight as a covariant. However, the fact that the correlation was not maintained when the lean subjects were examined separately tends to support the data from the present study, in which no effect of macronutrient composition on \( S_I \) was found in normal-weight individuals. The issue of the composition of the subjects’ diets before the study must also be considered when comparing the results of the study by Lovejoy et al (9) with those of the present study.

Interesting relations between insulin action and SMLPL activity after HC feeding were uncovered. An inverse correlation was seen between fasting glucose concentrations and SMLPL after 15 d of HC feeding, whereas the correlation between \( S_I \) measured by the euglycemic clamp technique and fasting SMLPL was positive. Thus, both an indirect and direct assessment of \( S_I \) was related to fasting SMLPL after 15 d of HC feeding. These SMLPL correlations were not seen after HF feeding, nor was fasting insulin or insulin-mediated glucose disposal correlated with fasting ATLPL after HC feeding. This relation between \( S_I \) after HC feeding in normal-weight subjects was similar to that seen by Pollare et al (43); however, in that study, correlations between \( S_I \) measured by the euglycemic clamp technique and fasting SMLPL were quantified across a wide range of insulin sensitivities (normal-weight and obese subjects with and without hyperinsulinemia and subjects with type 2 diabetes). A significant relation between insulin sensitivity and SMLPL was not seen in normal-weight subjects alone, nor was the previous dietary period controlled. Unlike after the HC diet, after the HF diet it was the change in SMLPL with the HF meal that was correlated with \( S_I \), not the fasting enzyme activity. The explanation for the difference between the effect of an HC compared with an HF diet on fasting SMLPL activity compared with the change in the enzyme after an HF meal is not readily apparent, but could relate to the effect of an HF meal after HF feeding on lipolysis in adipose tissue. In adipose tissue, HF feeding followed by an HF meal may permit sufficient fatty acids to be available locally to inhibit the heparin-releasable enzyme activity or displace it from endothelial binding sites (44, 45), thus, the decrease in the meal response. In muscle, these fatty acids may independently enhance SMLPL (46) and overcome the expected inhibitory effect of insulin (6).

The results of this study indicate that the tissue-specific regulation of LPL in adipose tissue and skeletal muscle is affected primarily by diet macronutrient composition rather than meal composition. The effects of both HC and HF diets and meals on postprandial changes in ATLPL activity were dependent on the preceding 15-d diet exposure, indicative of a necessary preparation period of the adipose tissue by the substrate mix. Although this was true after both diets, the HC diet allowed greater postprandial LPL response. Diet macronutrient composition was shown to affect the relations of LPL to measures of insulin action. Although basal activity levels of SMLPL were not directly affected by diet composition, fasting SMLPL after the HC diet was clearly affected by the degree of whole-body \( S_I \) after sustained HC intake. After the HF diet or meal, the associations between SMLPL and insulin action were evident only postprandially, perhaps indicating that the addition of an HF meal to an HF diet was required to saturate the fat fuel compartment before fuel metabolism could be forced in the direction of fat oxidation.

In summary, several weeks of HC compared with HF feeding in normal-weight subjects increased the responsiveness of ATLPL to an HC compared with an HF meal. However, the same diet exposure had no effect on fasting activity levels of ATLPL or SMLPL, the responsiveness of SMLPL to a meal, or \( S_I \). These data suggest that habitual dietary carbohydrate intake may have a stronger effect on subcutaneous fat storage than does the amount of dietary fat.

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