Negative Regulation of Leptin by Chronic High–Glycemic Index Starch Diet

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The response of plasma leptin to a high–glycemic index (high-GI) starch diet after a short (3 weeks) and prolonged (12 weeks) period was determined in Sprague-Dawley rats. Age-matched rats were fed an identical isocaloric diet except that the carbohydrates were from either mung bean starch (low-GI) or waxy cornstarch (high-GI). After a single test meal of the high-GI starch diet, postprandial plasma glucose ($P < .05$) and insulin ($P < .01$) peaks and plasma glucose ($P < .014$) and insulin ($P < .05$) areas were higher versus the low-GI starch diet (n = 8 per group). Other age-matched control rats were fed the same diets for a longer period. After 3 weeks, ob mRNA levels were decreased by 50% ($P < .005$) in the epididymal adipose tissue of high-GI–fed rats versus low-GI–fed rats, without a significant decrease in plasma leptin. After 12 weeks of the high-GI starch diet, both plasma leptin and ob mRNA were decreased by 34% ($P < .005$) and 41% ($P < .05$), respectively, compared with the low-GI diet. Both relative epididymal adipose tissue weight (adjusted per 100 g body weight) and total fat mass, as measured by dual-energy x-ray absorptiometry (DEXA), were unchanged by the high-GI starch diet. Basal nonfasting plasma insulin, glucose, and triglycerides were not altered by the high-GI starch diet, whereas free fatty acids were significantly elevated and associated with a trend ($P < .13$) for increased plasma free glycerol. Plasma leptin levels were negatively correlated with free fatty acid levels ($r = .56$, $P < .05$). Despite low leptin, rats fed on the high-GI diet did not increase their food intake, suggesting increased leptin sensitivity. These findings might precede weight gain and the increase in fat mass. Chronic nutritional factors might alter plasma leptin via several overlapping factors independently of energy intake.
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LEPTIN, the product of the ob gene,[1] is an adipose tissue–secreted protein that signals the magnitude of energy stores to the brain and regulates food intake and whole-body energy balance.[2,3] Plasma leptin levels and ob gene expression are correlated with adipose tissue mass in humans,[4] suggesting that adipose depot size is a major regulator of leptin production. However, accumulating evidence supports the concept that plasma leptin is determined by additional factors, including individual metabolic and hormonal status. In a stable situation, plasma leptin is thought to signal a set point where caloric intake and energy expenditure are balanced. This set point reflects a level of leptin sensitivity, which might vary according to genetic and/or environmental factors.

Little is known about the nutritional regulation of leptin production. Restriction and refeeding are known to regulate plasma leptin and ob gene expression in rodents and humans.[4,5] In these conditions at the extremes of energy balance, leptin concentrations are down regulated and upregulated,[3,6] respectively. The impact of increased dietary fat on circulating leptin has been assessed in several models. A high-fat diet produced a sustained increase in circulating leptin in both normal and transgenic mice after genetic ablation of brown adipose tissue, with leptin levels accurately reflecting the amount of body lipid across a broad range of body fat.[7] A high-fat diet also increased ob gene expression in adipose tissue of male Sprague-Dawley rats.[8] However, this does not prevent hyperphagia and obesity, suggesting that high-fat–fed rodents become resistant to leptin. A variation in the carbohydrate content of the diet might also regulate leptin levels. Recently, Jenkins et al.[9] demonstrated a pronounced decrease in serum leptin in association with reduced carbohydrate intake in humans before a substantial loss of body fat. They suggest a role for leptin in defending the body's carbohydrate stores.

We have previously demonstrated that changing the type of starch from a low to a high amylopectin content produces high postprandial plasma glucose and insulin peaks.[10] This nutritional manipulation was achieved by feeding rats a waxy cornstarch diet containing starch with 99.5% amylopectin (high–glycemic index [high-GI] starch) versus a diet with starch from mung bean with 68% amylopectin (low-GI starch). The repeated high postprandial glycemic and insulin peaks after 3 weeks of the high-GI starch diet increased lipogenesis,[10,11] suggesting a change in the adipose cell metabolic status. These observations prompted us to determine the response of leptin to this nutritional challenge.

MATERIALS AND METHODS

Rats and Diets

Forty normal male Sprague-Dawley rats (Centre d'Elevage Robert Janvier, Le Genest St-Isle, France) were used. The approval to use laboratory animals was given by the French Ministry of Agriculture, and the protocol complied with the National Institutes of Health (NIH) guidelines (NRC 1985) for the care and use of laboratory animals. At 5 weeks of age, rats (weighing 110 to 130 g) were randomly assigned for 3 or 12 weeks to one of two isocaloric, isoglucidic, and isolipidic diets containing 57.5% carbohydrate as either mung bean (low-GI) or waxy cornstarch (high-GI), as described by Kabir et al.[10] The composition of the diets is shown in Table 1. The mung bean starch was presented as cooked powdered Chinese noodles (Brand, Pagoda, Republic of China) purchased from local Asian supermarkets in France and prepared and offered by Nestlé (Orbe, Switzerland). The waxy cornstarch was prepared and offered by Cerestar Benelux (Breda, The Netherlands). The complete mixed diet (semisynthetic modified powder no. 210) was prepared by UAR (Usine d'Alimentation Rationnelle, Villemoisson-sur-Orge, France). Three or 4 rats were housed per cage, and daily food intake was determined by weighing the food remaining in the cage every 2 days. Rats were weighed once weekly.

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Table 1. Composition of Mung Bean (low-GI) Starch and Waxy Cornstarch (high-GI) Diets

Component (g/kg)	Mung Bean Starch (low-GI)	Waxy Cornstarch (high-GI)
Starch	575	575
Amylose (%)	32	0.5
Amylopectin (%)	68	99.5
Vegetable and animal fat	55	55
Casein	230	230
Mineral mix	70	70
Vitamin mix	10	10
Cellulose	60	60

Twenty-four rats were decapitated in the fed state between 8:30 and 9:30 AM (n = 12 per group) after 3 weeks and 16 rats (n = 8 per group) after 12 weeks. Free access to food was allowed till the time of decapitation. Thus, rats could be considered neither in a fasting state nor in a real postprandial state. Blood was collected, and the plasma was immediately separated by centrifugation. Samples were stored at −20°C for further nonfasting plasma leptin, glucose, insulin, free glycerol, and lipid measurements. Epididymal and retroperitoneal fat pads were immediately removed, weighed, and stored at −80°C for later gene expression studies.

Because decapitation of the rats and measurement of the plasma parameters in the chronic studies were performed in the nonfasting state (neither fasting nor postprandial), an additional group of 16 male Sprague-Dawley rats (150 to 170 g body weight) were used to determine the postprandial plasma glucose and insulin responses to a single test meal of each experimental diet. Rats were placed in individual polypropylene cages for sedentary animals under a 12-hour light/dark cycle at 24°C. Rats were trained for 2 weeks as follows. Each morning, a small amount of powdered standard commercial diet (semipurified diet no. 210 UAR) was placed in the cage and removed after 15 minutes. Rats then had free access to diet from 2:00 to 8:00 PM and were food-deprived overnight. By the end of the training period, rats were accustomed to eating a given amount of food within 15 minutes. After 2 weeks, 2 g of the 2 experimental diets were fed to the rats (200 to 220 g weight) that were food-deprived overnight. Rats were randomly assigned to 2 groups, each receiving 1 of the 2 test meals (high-GI or low-GI starch diets). Pentobarbital anesthesia was administered only to rats that consumed all of the offered food. Blood samples were taken from the tip of the tail after 30, 60, 90, 120, 150, and 180 minutes to measure plasma glucose levels. Fasting plasma glucose (0 minute) was determined on a separate day under similar conditions.

Measurement of Plasma Leptin, Glucose, Insulin, Free Glycerol, and Lipid Concentrations

Plasma leptin was determined in duplicate by a commercial radioimmunoassay kit (Linco Research, St. Charles, MO). Plasma glucose was determined by the glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin (Insulin RIA kits; CIS bio International, Gif sur Yvette, France), triglycerides (Enzymatic triglyceride kit; BioMérieux, Marcy-l'Etoile, France), cholesterol (Labintest Cholesterol kit; Labintest, Aix-en-Provence, France), phospholipids (Enzymatic phospholipid kits; BioMérieux), free fatty acids (Enzymatic free fatty acid kits, Nefa C*; Unipath, Dardilly, France), and free glycerol (Enzymatic Bioanalysis kit; Boehringer Mannheim, Meylan, France) were also measured. The plasma glycerol measurement was performed to determine only free glycerol (as an index of lipolysis) and not total glycerol that also includes glycerol due to triglyceride hydrolysis.

Measurement of Total Fat Mass

Total fat mass was measured by dual-energy x-ray absorptiometry (DEXA) using a QDR 4500 (Hologic, Waltham, MA).[12] These measurements were made 1 day before decapitation of the rats fed for 12 weeks on the experimental diets. Due to technical problems, only 5 rats in the diet group were used. Unfortunately, the apparatus was not available during the 3-week experiment.

Northern Blot Analysis of ob mRNA

Total RNA was extracted from frozen epididymal adipose tissue samples as described by Chomczynski and Sacchi,[13] using the RNA plus kit (Bioprobe Systems, Montreuil-Sous-Bois, France). Equal amounts (20 μg) of total RNA were applied to 1% agarose gel containing 0.66 mol/L formaldehyde, fractionated by electrophoresis, and transferred by capillarity onto nylon membrane (Positive membrane; Appligene, Illkirch, France). Hybridization was performed using an α[^{32}P]ATP-labeled mouse ob cDNA fragment spanning nucleotides +50 to +659.[14] The same blots were hybridized with an oligonucleotide specific for the 18S ribosomal RNA labeled with [^{32}P]ATP. Quantification was performed by scanning densitometry. Data are presented as the ratio of ob/18S mRNA signals.

Statistical Analysis

In the test meal study, the plasma glucose and insulin areas under the curve after the 2 test meals were compared by 1-way ANOVA. Overall comparisons among the 2 groups for the 3-week and 12-week studies were made separately by 1-way ANOVA to test the effect of diet. When the variances associated with each experimental mean were heterogeneous, a logarithmic transformation was performed. Linear regression analysis was applied to determine the correlation between plasma leptin and free fatty acids and adipose tissue mass. When the 2 experiments (3- and 12-week experiments) were analyzed together to evaluate the effect of duration and type of diet, a 2-way ANOVA was used. All analyses were performed with the Statview 512+ software program (Brainpower, Calabasas, CA). Results are given as the mean ± SEM. Differences were considered significant at a P level less than .05.

RESULTS

After a single test meal, the areas under the glucose and insulin response curves (180 minutes) were higher ($P < .014$ and $P < .05$, respectively) in rats that consumed the high-GI diet versus those that consumed the low-GI diet (Fig 1). The plasma glucose (8.3 ± 0.5 *v* 6.7 ± 0.6 mmol/L, $P < .05$) and

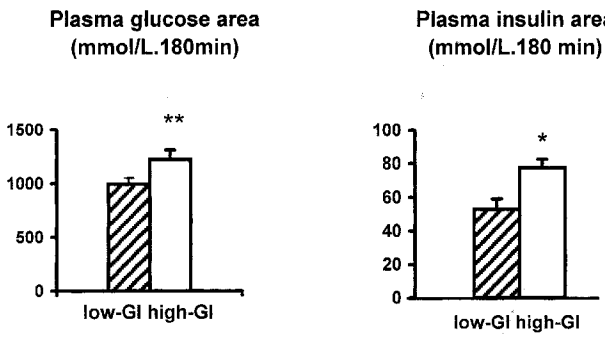

Fig 1. Area under the plasma glucose and insulin response curve after a test meal of either the mung bean (low-GI) or waxy cornstarch (high-GI) diet. The area under the glucose and insulin response curve (180 minutes) was higher ($P < .01$ and *$P < .05$, respectively) after the high-GI meal *v* the low-GI meal. Values are the mean ± SEM (n = 8).**

insulin (634 ± 49 *v* 456 ± 44 pmol/L, $P < .01$) peaks at 60 minutes were also higher after the high-GI meal compared with the low-GI meal (data not shown).

In a separate control group (Sprague-Dawley rats weighing 110 to 130 g fed for 3 weeks on a standard diet, n = 8) studied concurrently with the experimental groups of the present study and used to evaluate other factors involved in leptin regulation, the normal leptin level was 3.4 ± 0.03 ng/mL for a body weight of 297 ± 6 g, food intake of 25.5 ± 0.1 g/d, relative retroperitoneal fat mass of 0.8% ± 0.1%, epididymal fat mass of 0.8% ± 0.1%, and total fat 17% (measured by DEXA). Unfortunately, there was no control group in the laboratory rats fed a standard diet for 12 weeks.

Characteristics of the rats fed the high-GI or low-GI diets for 3 or 12 weeks are shown in Table 2. Food intake, body weight, and relative adipose tissue weight were not significantly different between the 2 dietary groups (low-GI *v* high-GI at either 3 or 12 weeks by 1-way ANOVA). In good agreement with the lack of change in adipose tissue and body weight, the percent of total fat mass per 1 kg body weight as assessed by DEXA after 12 weeks (n = 5 rats per group) was not significantly different between the 2 groups (Table 2). After 3 weeks, there was no change (high-GI *v* low-GI) in nonfasting plasma glucose (7.88 ± 0.24 *v* 7.51 ± 0.41 mmol/L, respectively), insulin (363 ± 28 *v* 415 ± 66 pmol/L), or plasma triglycerides (1.08 ± 0.21 *v* 1.32 ± 0.11 mmol/L), as previously reported.[10,11] After 12 weeks, at the time of decapitation, nonfasting plasma glucose (6.66 ± 0.34 *v* 6.99 ± 0.27 mmol/L) and nonfasting plasma insulin (300 ± 14.60 *v* 330 ± 8.40 pmol/L) were similar in the 2 groups (high-GI *v* low-GI, respectively), as well as plasma triglycerides (1.69 ± 0.25 *v* 1.50 ± 0.18 mmol/L), phospholipids (0.57 ± 0.15 *v* 0.74 ± 0.24 mmol/L), and cholesterol (2.45 ± 0.26 *v* 2.50 ± 0.15 mmol/L). In contrast, plasma free fatty acid concentrations were significantly higher (Fig 2) and plasma free glycerol showed a tendency to be higher (346 ± 108 *v* 202 ± 37 μmol/L, $P < .13$ after logarithmic transformation) in rats fed the high-GI diet versus the low-GI diet.

When changes from 3 to 12 weeks were examined in both high-GI and low-GI groups (2-way ANOVA, effect of duration and effect of diet), a duration effect was found, most probably an effect of age. Older rats in the 12-week experiment were heavier ($P < .0001$) and had a heavier epididymal fat weight ($P < .0001$), higher food intake ($P < .001$), and lower energy efficiency ($P < .001$) than younger rats in the 3-week experiment, as expected (Table 2). These changes (3 weeks *v* 12 weeks) were associated with a decrease in plasma free fatty acids (from 0.503 ± 0.085 to 0.221 ± 0.020 mmol/L in the low-GI group and 0.615 ± 0.168 to 0.384 ± 0.046 mmol/L in the high-GI group, $P < .05$) but an increase in plasma leptin (from 3.5 ± 0.4 to 6.0 ± 0.5 ng/mL in the low-GI group and 2.2 ± 0.4 to 3.9 ± 0.3 ng/mL in the high-GI group, $P < .0001$).

The analysis of ob gene expression by Northern blot showed that 3 weeks of feeding the high-GI diet induced a marked decrease (−50%) in ob mRNA in epididymal adipose tissue ($P < .005$, Fig 2). This diet-induced effect persisted after 12 weeks at the same magnitude ($P < .05$). Plasma leptin concentrations were not significantly changed in rats fed the high-GI diet for 3 weeks, whereas after 12 weeks, they were decreased by 34% ($P < .005$). In addition, at 12 weeks, there was a negative correlation between plasma leptin and free fatty acids ($r = .56$, $P < .05$; Fig 3) but not with adipose tissue mass (epididymal and retroperitoneal). There was no correlation between plasma leptin and free fatty acids at 3 weeks. When all rats (3- and 12-week experiments) were grouped together, a negative correlation was found between plasma leptin and free fatty acids ($r = .54$, $P < .01$).

DISCUSSION

Our data demonstrate for the first time that the type of dietary carbohydrate influences both ob gene expression and the circulating leptin level. Twelve weeks of a high-GI starch diet, as compared with a low-GI starch diet, decreased serum leptin in normal Sprague-Dawley rats. A decrease in ob gene expression in epididymal adipose tissue was already apparent after 3 weeks of the high-GI starch diet. The lag time between

Table 2. Food Intake, Body Weight, and Epididymal Adipose and Retroperitoneal Tissue Weight in Rats After 3 and 12 Weeks on Diets Containing 575 g/kg Mung Bean Starch or Waxy Cornstarch

	3 Weeks		12 Weeks	
Parameter	Mung Bean Starch	Waxy Cornstarch	Mung Bean Starch	Waxy Cornstarch
Food intake (g · rat · d^{-1})	23 ± 0.4	22 ± 0.2	27 ± 0.5	26 ± 1.2‡
Body weight (g)	307 ± 8	289 ± 7	494 ± 14	458 ± 18‡
Energy efficiency*	0.370 ± 0.012	0.352 ± 0.019	0.236 ± 0.012	0.223 ± 0.011‡
Body weight gain (g)	182.8 ± 8.6	161.7 ± 6.4	382 ± 14	347 ± 17
Epididymal fat weight				
Relative (g · 100 g body $weight^{-1}$)	0.77 ± 0.04	0.67 ± 0.04	1.14 ± 0.06	0.99 ± 0.06‡
Absolute (weight 2 pads, g)	2.28 ± 0.17	1.90 ± 0.15	5.65 ± 0.34	4.25 ± 0.30†‡
Retroperitoneal fat weight				
Relative (g · 100 g body $weight^{-1}$)	ND	ND	1.62 ± 0.13	1.38 ± 0.12
Absolute (weight 2 pads, g)	ND	ND	8.05 ± 0.74	6.21 ± 0.46
Total fat %§	ND	ND	16.7 ± 1.1	15.4 ± 1.6

NOTE. Values are the mean ± SEM (n = 8-12).

Abbreviation: ND, not determined.

*Ratio of weight gain to energy intake (g/g diet).

†There were significant differences between mung bean starch and waxy cornstarch after 12 weeks, $P < .05$ by 1-way ANOVA.

‡For the 2 experiments together, there was a significant effect of the duration of the diet, $P < .0001$ by 2-way ANOVA.

§Measured by DEXA.

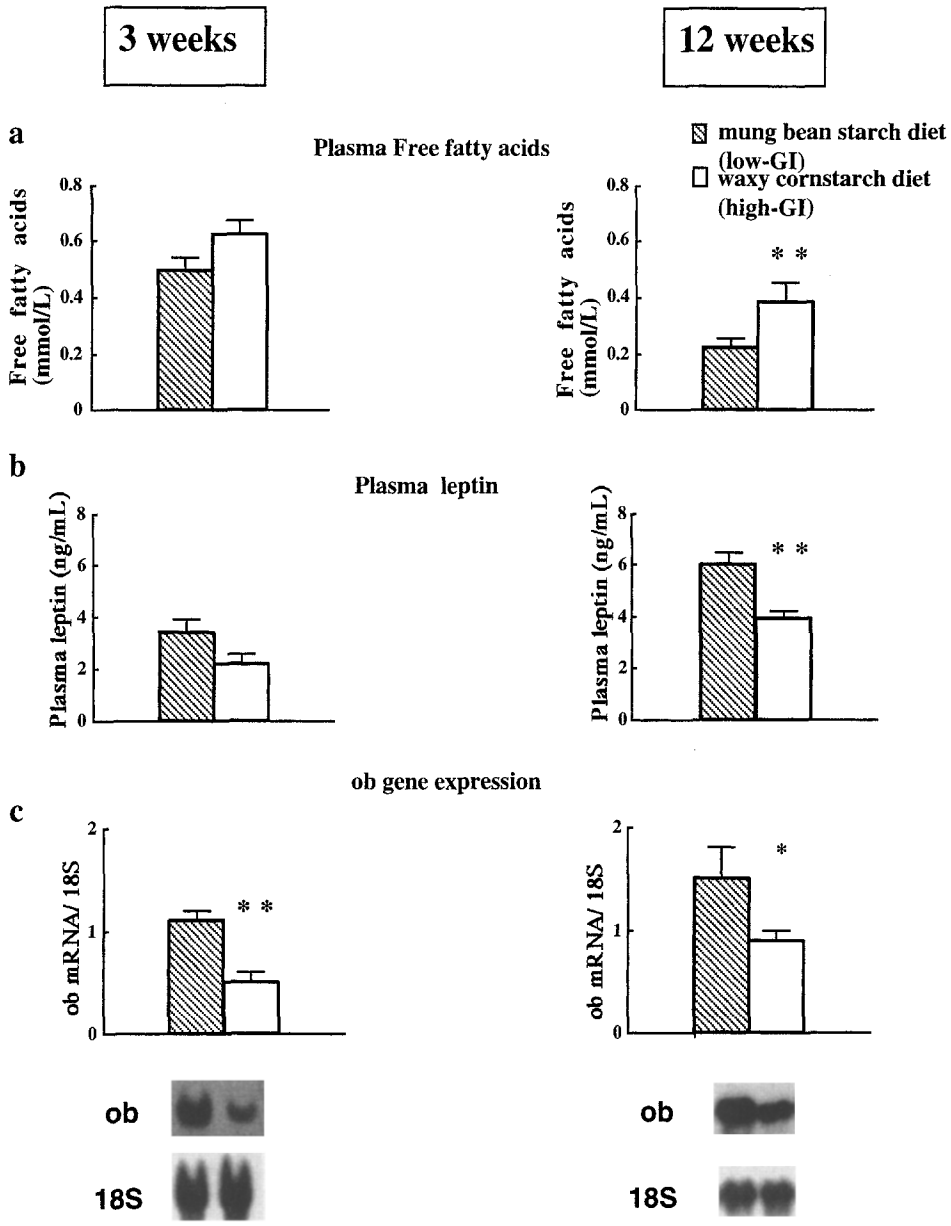

Fig 2. (A) Plasma free fatty acid concentration, (b) plasma leptin concentration, and (c) ob mRNA in epididymal adipose tissue of rats consuming either the mung bean (low-GI) or waxy cornstarch (high-GI) diet for 3 or 12 weeks. The high-GI diet decreased ob mRNA in epididymal adipose tissue after 3-week ($P < .005$) and 12-week (*$P < .05$) diet *v* the low-GI diet. Plasma leptin decreased significantly (*$P < .005$) after 12 weeks of the high-GI diet *v* the low-GI diet. The modifications induced by the high-GI diet were associated with an increase in plasma free fatty acid at 12 weeks (**$P < .005$).**

decreased epididymal ob mRNA and decreased plasma leptin might be due to a difference in the responsiveness of the various fat depots. Indeed, ob mRNA levels were measured only in the epididymal adipose site, which might be more sensitive to the diet effect than other adipose pads. In addition, the quantitative contribution of the individual fat pad to plasma leptin is not known. Our observations are compatible with epididymal adipose tissue contributing only a fraction of the total leptin production which determines the plasma leptin level. Although not demonstrated in this study, it is likely that after 12 weeks ob gene expression is decreased in several adipose tissue sites, thus ensuring decreased plasma leptin in high-GI starch rats. These results might also suggest that other tissues are involved in the regulation of plasma leptin. Recently, it has been demonstrated that the stomach is a source of leptin.[15] Thus the regulation of plasma leptin might be under the control of both adipose tissue and the stomach secretions.

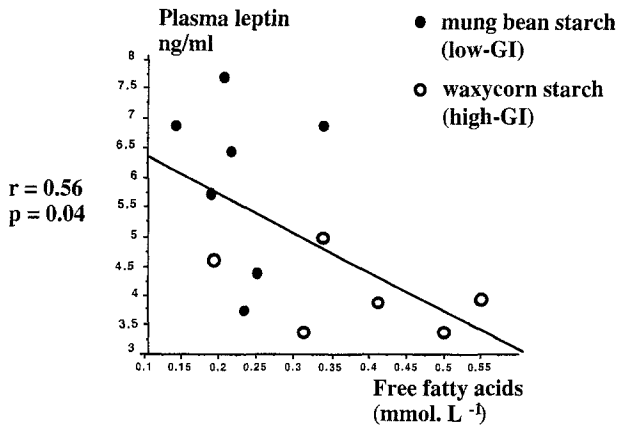

Fig 3. Correlation between plasma leptin and free fatty acids at 12 weeks.

Adipose tissue ob mRNA and plasma leptin levels correspond very closely to the amount of adipose tissue in rodents and humans.[4] Changes in plasma leptin and epididymal adipose tissue ob gene expression at the given times (3 or 12 weeks) in the present study were not accompanied by any change in food intake, body weight, or relative (% of body weight) epididymal and retroperitoneal adipose tissue weight. Moreover, we showed previously that there was only a slight difference in the resistant starch content (10.7% ± 0.7% *v* 0%) and the α-amylase digestibility in vitro (45.5% ± 3% *v* 60.1% ± 4% per 30 minutes) of the low-GI and high-GI starches, respectively.[10] These findings suggest that diet-induced changes in plasma leptin and ob gene expression at a given time could occur independently of major changes in adipose tissue mass and of energy availability or digestibility. However, we could not ignore the well-known effect of age. The older rats were heavier, and the increased adipose tissue weight was associated with an increase in both plasma leptin and ob mRNA. These modifications were associated with a decrease in energy efficiency (Table 2). Thus, the factors involved in the regulation of leptin by age might be totally different from those implicated in the regulation of leptin at a given time by nutritional factors.

The present results are not in opposition to the lipostat hypothesis, but strengthen the implication of biological factors other than adipose tissue size in determining plasma leptin levels. Insulin or some components of insulin resistance are possible candidates. In the present study and in previous studies,[10,11] a high-GI diet was demonstrated to induce high postprandial plasma glucose and insulin peaks. Although not consistently found,[14,16,17] a stimulatory effect of insulin on ob gene expression has been reported by several groups.[3,6,18] However, in the present study, the high-GI diet that increased postprandial insulin secretion is actually associated with decreased leptin levels. This apparent contradiction might be due to the presence of insulin resistance in these rats. Chronic consumption of a high-GI starch diet in rats was shown to induce first (3 weeks) a decrease in insulin-stimulated glucose oxidation in adipocytes[10] and an increase in whole-body insulin resistance later on (8 weeks).[19] Few data are available on the association of leptin levels and insulin sensitivity and are somewhat contradictory. Leptin levels have been found to be higher in lean[20] and slightly overweight normoglycemic[21] insulin-resistant men, but no association between leptin levels and non–insulin-dependent diabetes mellitus (NIDDM) has been observed.[22] However, in other reports, the effect of insulin on leptin production was found to be diminished with insulin resistance. During a euglycemic-hyperinsulinemic clamp in normal subjects, the insulin-induced increase in leptin correlated positively with insulin sensitivity in normal healthy men.[23] Consequently, plasma leptin could be inappropriately low for a given fat mass or caloric intake in insulin-resistant subjects. It was also found that while serum leptin is increased in the insulin-resistant offspring of NIDDM patients, insulin-stimulated glucose uptake significantly contributes to the leptin level as assessed by multiple regression, indicating an association between the increase in leptin and the increase in insulin sensitivity.[24] In the present study, the presence of insulin resistance might be a time-dependent effect of the high-GI diet and might explain the decrease of leptin production in the face of such a diet.

Another factor to be considered is the increase in plasma free fatty acids in rats consuming the high-GI diet. The implication of free fatty acids in the regulation of leptin production or expression is supported by some arguments in the literature: It has been previously suggested that plasma leptin is sensitive to free fatty acids. Indeed, in vitro, free fatty acids were found to exert a concentration-dependent inhibition of leptin transcription in adipocytes.[25] In rodents, conditions known to increase lipolysis, thus increasing free fatty acids, such as cold exposure and starvation are associated with decreased leptin gene expression.[26] In humans, Landt et al[27] reported decreased plasma leptin levels at the extremes of the exercise-induced negative balance that are associated with an increase in fat mobilization. In keeping with this, Donahoo et al[28] demonstrated that increasing free fatty acids by infusion of isoproterenol in humans decreases the leptin concentration. In the present study, the implication of free fatty acids in the regulation of leptin levels is supported by the presence of a negative relationship between plasma free fatty acid and leptin levels at 12 weeks, suggesting that the high-GI starch diet effect might be mediated at least in part by an inhibitory effect of free fatty acids on leptin production. In addition, the increase in leptin from 3 to 12 weeks was also associated with a decrease in free fatty acids, indicating that leptin regulation by age could be mediated also by the plasma level of free fatty acids.

Whatever the mechanism, the decrease in plasma leptin by a high-GI starch diet is in agreement with the concept that high-GI diets, which produce postmeal high plasma insulin and glucose peaks, are less satiating than low-GI diets.[29] Increasing low-GI foods may preserve leptin levels and hence reduce the appetite and lead to a better compliance, whereas high-GI starchy foods could decrease satiety and increase appetite. This hypothesis is supported by the recent finding that administration of the biologically active carboxy-terminal end of cholecystokinin (a satietogenic factor) resulted in a rapid increase of leptin secretion by gastric fundic mucosa.[15] The cholecystokinin level was demonstrated to be inversely proportional to the glycemic and insulin response to carbohydrate foods.[29] Thus, high-GI foods might decrease cholecystokinin and thus leptin secretion and satiety. Although a high-GI diet was not associated with increased food intake, it cannot be excluded that food intake, weight gain, and fat mass might increase later on. Pawlak et al[30] demonstrated that a higher-GI diet (pure glucose) than ours increases fat mass and body weight in rats after longer periods (16 weeks) than those used in our study. Our hypothesis is supported by the findings of Ravussin et al,[31] who demonstrated that relatively low plasma leptin concentrations precede weight gain in obese insulin-resistant Pima Indians. This is likely, because with unpublished results from our laboratory (Bouche C, Rizkalla SW, Slama G, 1999), we showed in normal men that when a chronic high-GI diet is able to increase abdominal adipose tissue mass, an increase in ob gene expression also follows. These results confirm that the reduction in leptin levels after 12 weeks of a high-GI diet under the present study conditions might only be due to the time lag that precedes

the increase in fat mass and the subsequent increase in leptin levels.

On the other hand, the results of the present study might suggest that the nutritional challenge has reset the plasma leptin concentration at a lower level, signaling an equilibrium situation where whole-body energy is balanced. This might reflect an increase in leptin sensitivity via a mechanism that remains to be determined. At variance with the different settings of plasma leptin observed in lean and obese individuals, which are strongly correlated with body fat mass, the high-GI starch diet–induced alteration in leptin sensitivity occurred at the same level of body fat. This suggests that the potential setpoint of leptin sensitivity is not necessarily linked to adiposity and might be altered by several dietary-induced biological factors, including free fatty acid variations.

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