Differential Effects of Fat and Sucrose on the Development of Obesity and Diabetes in C57BL/6J and A/J Mice

R.S. Surwit, M.N. Feinglos, J. Rodin, A. Sutherland, A.E. Petro, E.C. Opara, C.M. Kuhn, and M. Rebuffé-Scrive

We have previously demonstrated that the C57BL/6J (B/6J) mouse will develop severe obesity, hyperglycemia, and hyperinsulinemia if weaned onto a high-fat, high-sucrose (HH) diet. In the present study, we compared the effects of fat and sucrose separately and in combination on diabetes- and obesity-prone B/6J and diabetes- and obesity-resistant A/J mice. After 4 months, the feed efficiency ([FE] weight gained divided by calories consumed) did not differ across diets in A/J mice, but B/6J mice showed a significantly increased FE for fat. That is, B/6J mice gained more weight on high-fat diets without consuming more calories than A/J mice. The increase in FE was related to adipocyte hyperplasia in B/6J mice on high-fat diets. Fat-induced obesity in B/6J mice was unrelated to adrenal cortical activity. In the absence of fat, sucrose produced a decreased in FE in both strains. Animals fed a low-fat, high-sucrose (LH) diet were actually leaner than animals fed a high–complex-carbohydrate diet. Fat was also found to be the critical stimulus for hyperglycemia and hyperinsulinemia in B/6J mice. In the absence of fat, sucrose had no effect on plasma glucose or insulin. These data clearly show that across these two strains of mice, genetic differences in the metabolic response to fat are more important in the development of obesity and diabetes than the increased caloric content of a high-fat diet.

MUCH OF THE ANIMAL research on genetic determinants of obesity has been based on a number of mutant strains of rodents. These strains develop severe obesity on both high-fat diets and laboratory chow, which is low in fat.[1] However, most human obesity is thought to occur in response to high-fat diets.[2,3] Differential weight gain in various mouse strains in response to diets rich in fat and sucrose has been demonstrated by our group[4-6] and by others.[7-9] These effects appear to be due to multiple genetic factors[5,10] and are not dependent on excess energy intake.[6,7] One strain that is particularly sensitive to the effects of diet on weight is the C57BL/6J (B/6J) mouse.[4-7,10] It will develop severe obesity, hyperglycemia, and hyperinsulinemia when raised on a high-fat, high-sucrose (HH) diet.[4-6] In response to such diets, B/6J mice not only become more obese generally, but show a particular increase in mesenteric (MES) fat cell number in comparison to the diabetes-resistant A/J strain.[6] Because diabetes and obesity have previously been induced in B/6J mice by a HH diet, it was not clear whether both fat and sucrose are necessary for obesity and diabetes to occur in B/6J mice.[4-7,10]

Several current theories exist to explain the role of fat in the development of obesity.[11,12] Fat has also received recent attention as the possible stimulus for the onset of type II diabetes in susceptible individuals.[13] Randle et al[14] described the glucose–fatty acid cycle, in which glucose uptake and oxidation are inhibited if fatty acid oxidation is operative. In fact, high-fat diets have been shown to produce hyperglycemia in pancreatically compromised mice,[15] and desensitization of pancreatic islets by fatty acids has been observed in isolated-islet preparations.[16,17]

Although fat has been ascribed a putative role in the development of both obesity and diabetes, Nuttall and Gannon[18] concluded that there is little evidence to implicate sucrose in either disorder. A recent epidemiologic study provided no evidence that dietary sucrose content was related to the onset of diabetes.[19] The present series of experiments was designed to determine the relative roles of fat and sucrose in the development of obesity and diabetes in the B/6J model. A further goal of this study was to assess more carefully the role of food intake in the development of obesity in the B/6J mouse to determine if the differential obesity that develops in this strain is related to diet-induced hyperphagia.

MATERIALS AND METHODS

One hundred B/6J and 100 A/J male mice were obtained from Jackson Laboratories (Bar Harbor, ME) at 4 weeks of age. Animals were housed five per cage in a temperature-controlled room with a 12-hour light/dark cycle. They were allowed ad libitum access to water and one of four diets as follows: 20 mice from each strain were fed either a HH or high-fat/low-sucrose (HL) diet, and 30 mice from each strain were fed either a low-fat/high-sucrose (LH) or low-fat/low-sucrose (LL) diet. All diets contained 16% protein and met American Institute of Nutrition requirements for mice with regard to mineral and vitamin content.[20,21] Diets were manufactured by Research Diets (New Brunswick, NJ). The composition of the diets is listed in Table 1.

Animals were maintained on these diets for 4 months. Body weight was determined biweekly. To avoid the stress of individual housing, food intake was measured on a per-cage basis for 24 hours once per week. Caloric content of food intake was determined based on 5.55 kcal/g for high-fat diets and 4.07 kcal/g for low-fat diets. The feed efficiency (FE) [(weight gained/kcal consumed) × 100] was determined after 16 weeks on the respective diets for each of 40 cages.

From the Departments of Psychiatry and Behavioral Sciences, Medicine, and Surgery, and the Sarah W. Stedman Nutrition Center, Duke University Medical Center, and Department of Psychology: Social and Health Sciences, Duke University, Durham, NC; and Department of Psychology, Yale University, New Haven, CT.

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Address reprint requests to R.S. Surwit, PhD, Box 3842, Duke University Medical Center, Durham, NC 27710.

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Table 1. Composition of the Four Diets

	LL	LH	HL	HH
kcal/g	4.07	4.07	5.55	5.55
Ingredients (g/kg)				
Casein	167.0	167.0	167.0	167.0
DL-Methionine	1.5	1.5	1.5	1.5
Maltodextrin 10	124.0	124.0	124.0	124.0
Corn starch	611.0	0.0	128.0	0.0
Sucrose	0.0	611.0	0.0	128.0
Soybean oil	18.3	18.3	18.3	18.3
Coconut oil, hydrogenated	29.3	29.3	244.0	244.0
Salt mix	29.3	29.3	29.3	29.3
Sodium bicarbonate, 27.4% Na	7.7	7.7	7.7	7.7
Potassium citrate, $1H_2O$, 36.2% K	2.9	2.9	2.9	2.9
Vitamin mix	7.3	7.3	7.3	7.3
Choline bitartrate	1.5	1.5	1.5	1.5
Yellow dye FD&C no. 5	0.07	0.00	0.00	0.00
Blue dye FD&C no. 1	0.00	0.07	0.04	0.00
Red dye FD&C no. 40	0.00	0.00	0.04	0.07

Abbreviation: FD&C, Food, Drug and Cosmetic.

Blood was collected at monthly intervals for 4 months beginning after 1 month's exposure to the diets. Blood was drawn after an 8-hour fast via retro-orbital sinus puncture in nonanesthetized animals. Plasma glucose concentration was determined using a Beckman Glucose Analyzer 2 (Fullerton, CA). Plasma insulin was measured with a double-antibody radioimmunoassay kit based on a rat standard (Linco Research, St Louis, MO). In addition, plasma corticosterone levels were determined in the morning under basal conditions and after a brief stress (shaking) at month 4 in 10 animals per strain per diet.[22]

After 4 months on the diets, 60 mice from each strain were shipped to Yale University for determination of fat pad weight, fat cell size, fat cell number, lipoprotein lipase activity (LPL), and basal and norepinephrine-stimulated lipolysis. Mice were maintained on their respective diets for 3 to 5 days before beginning the experiments. Since animals were less fat on low-fat diets, it was necessary to use twice the number of mice and to pool fat from two animals from these groups to obtain enough fat to perform both the LPL and lipolysis assays. Therefore, 10 mice from each strain on high-fat diets and 20 mice from each strain on low-fat diets were used. Subcutaneous (inguinal [ING]) and visceral (MES) fat pads were carefully dissected from each animal according to defined anatomic landmarks. All subcutaneous fat between the lower part of the rib cage and the mid-thigh was considered ING fat, whereas all fat along the mesentery starting at the lesser curvature of the stomach and ending at the sigmoid colon was considered MES fat. Each fat pad was weighed and sampled for fat cell size, LPL activity, and basal and norepinephrine-stimulated lipolysis. Fat cell size and lipolytic measurements were performed on isolated adipocytes from the stroma by incubation of the fragments in medium 199 (Gibco BRL, Grand Island, NY) that contained 4% (wt/vol) albumin and 1.5 mg/mL collagenase (Sigma Chemical, St Louis, MO) for 60 minutes at 37°C as previously described.[23] After filtration through a nylon mesh (250 μm), cells were carefully washed four times and suspended in fresh medium. Aliquots (100 μL) from the cell suspension, lipocrit 20% to 25%, were added to siliconized bottles that contained 2 mL medium 199 with 4% albumin with or without norepinephrine (10^{-7} to 10^{-4} mol/L; Sigma Co) as indicated. Control experiments have shown that under these incubation conditions with a low lipocrit (1% to 2%), glycerol release remains linear for at least 3 hours. After a 2-hour incubation at 37°C and pH 7.4, cells and medium were transferred to soft plastic tubes and centrifuged through silicone oil to separate cells and incubation medium as described by Gammeltoft and Gliemann.[24] Glycerol content of the medium was analyzed enzymatically[25] and taken as an index of lipolysis. An aliquot of the suspension was used to determine immediately the diameter of at least 100 cells using a microscope according to the method reported by Smith et al.[23] Fat cell volume was calculated according to the following formula: $v = \pi([3 \cdot SD^2 \cdot d] + d^3)/6$, where d is the mean fat cell diameter and SD is the standard deviation. Fat cell weight was obtained using the assumption that the density of the fat cell is 0.915. Triglyceride was extracted from fat tissues according to the method reported by Dole and Meinertz,[26] and fat cell number was estimated using triglyceride tissue content and fat cell weight. LPL activity was determined after heparin elution, using a stable ^{3}H-triolein emulsion according to the method reported by Nilsson-Ehle and Schotz.[27] Released free fatty acids were separated by liquid-liquid partition as described by Gammeltoft and Gliemann.[24] LPL activity was expressed as units (micromoles of free fatty acids released per hour) per number of cells. A logarithmic transformation of fat depot weight, fat cell weight, fat cell number, LPL activity, and lipolysis was used to reduce skewness and equalize variances for analysis. Data were analyzed with a two-way ANOVA. The Scheffe test was used to determine differences in the means of body weight, glucose, insulin, corticosterone, and FE. The Bonferroni t test was used to determine differences in the means of fat depot weight, fat cell weight, fat cell number, LPL activity, and lipolysis.

Because sucrose has been shown to induce obesity in rats when given via drinking water,[28] a second experiment was undertaken in which 10 A/J and 10 B/6J mice were raised on the LL diet described earlier and allowed ad libitum access to plain water, and an additional 10 animals per strain were given the same solid diet (LL) and access to a 16% solution of sucrose in water. Because of the small number of animals in this study, food consumption was determined individually. For one 24-hour period per week, animals were housed individually. Food and water consumption was measured for that period. Caloric intake was determined based on 4.07 kcal/g diet and 0.64 kcal/mL 16% sucrose solution. After 4 months, FE was determined as described earlier. Glucose, insulin, and FE data were analyzed.

RESULTS

Experiment I

Body weight. ANOVA showed a significant effect of strain ($F_{1,189} = 142.4$, $P < .0001$) and diet ($F_{3,189} = 142.3$, $P < .0001$), as well as an interaction of strain versus diet ($F_{3,189} = 32.1$, $P < .0001$). As listed in Table 2, all animals on either high-fat diet were heavier than animals on low-fat diets. However, fat and complex carbohydrate differentially affected B/6J and A/J animals. Whereas the weights of B/6J and A/J animals on LH and LL diets were similar, B/6J animals on HH and HL diets were heavier. B/6J animals on high-fat diets were 50% heavier than A/J animals on high-fat diets ($P < .0001$).

Caloric intake. There was a significant main effect for diet ($F_{3,24} = 32.1$, $P < .0001$). Animals that were fed high-fat diets consumed more calories than animals on low-fat diets. There were no differences in caloric consumption between HH and HL diets or between HL and LL diets (Table 2).

FE. There was a significant interaction between strain and diet in FE (weight gain divided by calories consumed) ($F_{3,24} = 7.98$, $P < .0007$). Post hoc comparisons indicate

Table 2. Body Weight, Caloric Intake, and Corticosterone Levels of A/J and B/6J Mice by Diet Groups

Strain	Body Weight (g)	Caloric* Intake (kcal)	Corticosterone (ng/mL) Basal	Corticosterone (ng/mL) Stress
A/J				
HH	33.3 ± 1.1	187.01 ± 5.96	32.41 ± 2.43	67.76 ± 9.73
HL	32.6 ± 0.9	173.27 ± 6.93	23.95 ± 4.52	81.70 ± 4.61
LH	26.0 ± 0.4	138.56 ± 6.47	20.64 ± 1.38	86.06 ± 12.57
LL	28.9 ± 0.7	144.20 ± 6.10	28.30 ± 5.71	50.17 ± 9.34
B/6J				
HH	46.4 ± 0.9	188.87 ± 3.80	29.09 ± 4.07	67.87 ± 6.34
HL	42.5 ± 1.3	196.58 ± 9.74	23.08 ± 3.76	61.21 ± 5.72
LH	26.9 ± 0.4	138.69 ± 3.85	29.07 ± 2.45	44.40 ± 6.89
LL	30.6 ± 0.5	147.82 ± 6.49	20.22 ± 3.12	50.84 ± 2.71

*Total of recorded caloric consumption. Caloric consumption was measured for a 24-hour period each week.

that although FE was similar in A/J and B/6J animals on low-fat diets, FE of fat was greater in B/6J than in A/J mice (Fig 1).

Fat distribution. There were main effects for diet in ING fat pads ($F_{3,71} = 60.4$, $P < .0001$) and MES fat pads ($F_{3,70} = 57.0$, $P < .0001$). There was also a main effect of strain in ING fat ($F_{1,71} = 7.0$, $P < .01$). An interaction between strain and diet was found for both MES ($F_{1,71} = 19.5, P < .0001$) and ING ($F_{1,71} = 19.6, P < .0001$) fat pad weights when data were expressed as absolute values. Similar results were obtained when data were expressed as relative values, as a percentage of body weight (data not shown). Group comparisons showed that fat content of the diet played a major role in determination of differences in fat pad weights between B/6J and A/J mice. As shown in Fig 2, in both high-fat diet groups ING and MES fat pads were larger in B/6J than in A/J mice ($P < .01$), whereas both pads were smaller in B/6J mice than in A/J mice on low-fat diets (LH, $P < .05$; LL, $P < .01$). In addition, only in B/6J mice did sucrose content

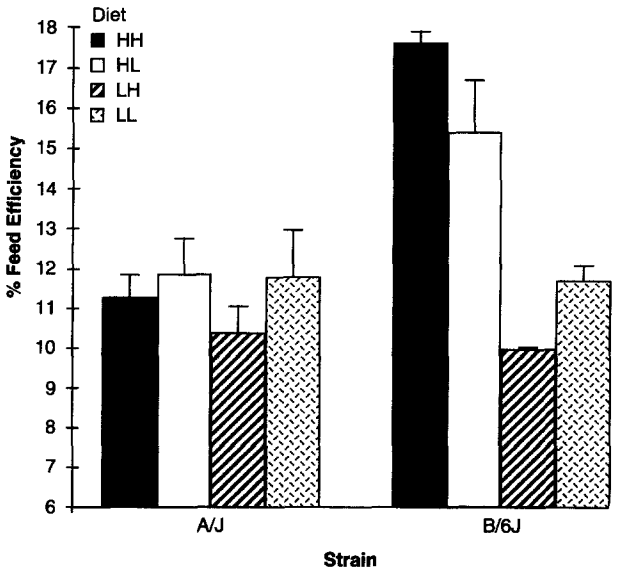

Fig 1. FE of A/J and B/6J mice (± SEM) on four different diets.

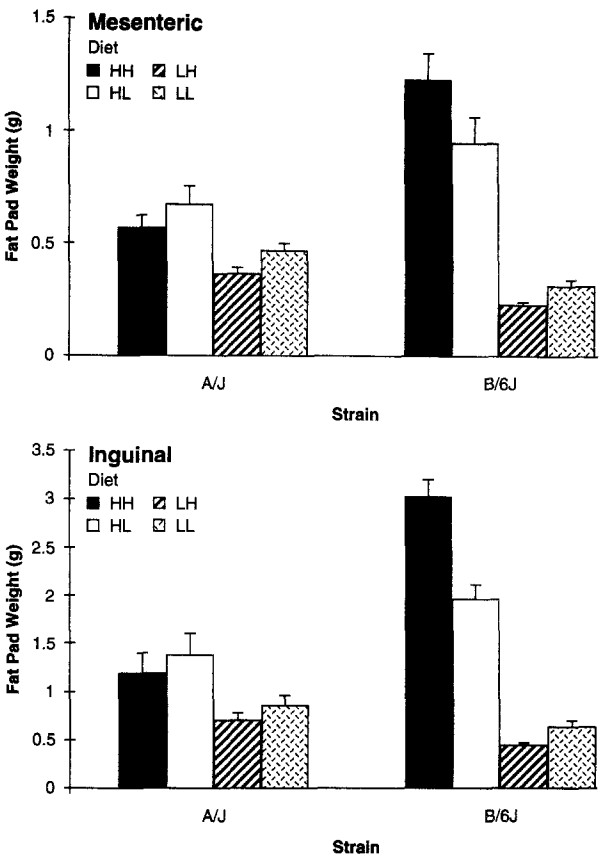

Fig 2. Fat pad weight in A/J and B/6J mice (± SEM) on four different diets.

of the diet seem to influence the size of fat pads, depending on the association of sucrose with high fat content in the diet. Within high-fat diet groups, sucrose exacerbated the effects of fat ($P < .01$ for ING, $P < .05$ for MES), whereas it had the opposite effect in B/6J mice on low-fat diets ($P < .05$, ING and MES).

Fat cell size. There were main effects for diet in both ING tissue ($F_{3,71} = 50.0$, $P < .0001$) and MES tissue ($F_{3,69} = 40.0, P < .0001$) and for strain in MES ($F_{1,69} = 12.1$, $P < .001$). An interaction for strain and diet was found for both MES ($F_{3,69} = 7.9$, $P < .0001$) and ING ($F_{3,71} = 10.7$, $P < .0001$) fat cell sizes, expressed as fat cell weights. Figure 3 shows that only the HH diet increased ING adipocyte size in B/6J mice as compared with A/J mice. In contrast, B/6J mice fed either low-fat diet had smaller fat cells in ING and MES depots ($P < .01$) as compared with A/J mice. The LH diet decreased fat cell size in MES adipose tissue ($P < .05$) in B/6J mice, but not in A/J mice.

Fat cell number. Main effects for strain were observed in both ING ($F_{1,71} = 12.1$, $P < .001$) and MES ($F_{1,70} = 20.0$, $P < .001$). Main effects for diet were also found in ING ($F_{3,71} = 4.1, P < .01$) and MES ($F_{3,70} = 3.7, P < .02$). There was also a significant interaction between strain and diet for fat cell number in MES ($F_{3,70} = 3.72$, $P < .02$) but not in ING fat pads. In both high-fat diet groups, the number of MES fat cells was increased in B/6J mice in comparison to A/J mice ($P < .05$; Fig 4). Sucrose did not affect fat cell

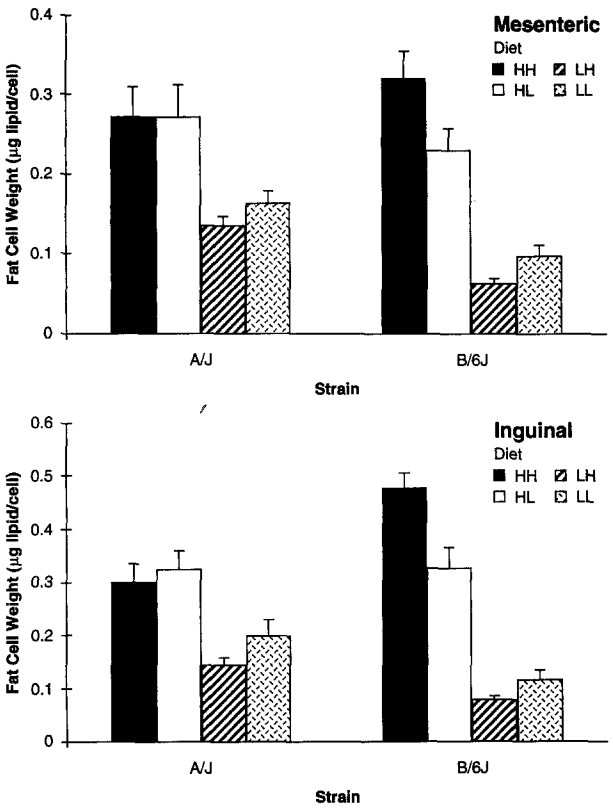

Fig 3. Fat cell size (weight) in A/J and B/6J mice (± SEM) on four different diets.

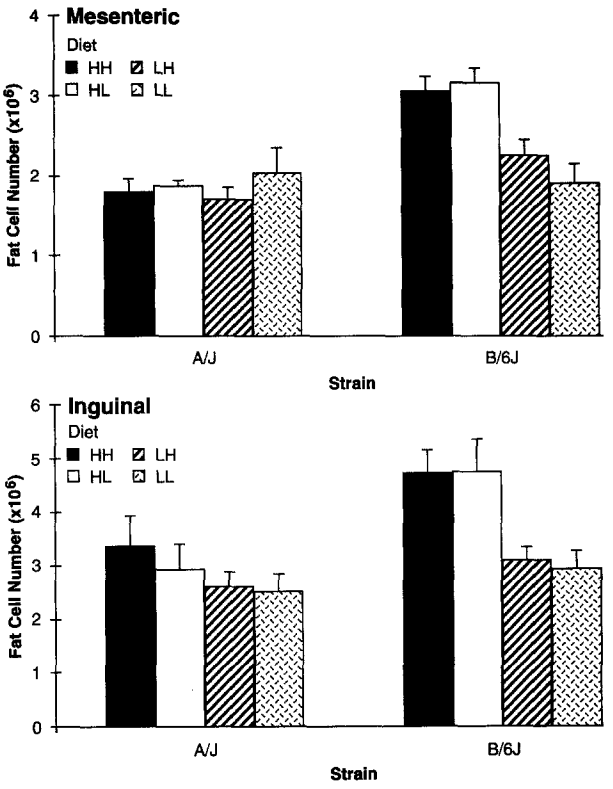

Fig 4. Fat cell number in A/J and B/6J mice (± SEM) on four different diets.

number, and no differences were observed between strains on low-fat diets.

LPL activity and lipolysis. Fat accumulation (LPL activity) and fat mobilization (basal and norepinephrine-stimulated lipolysis) were determined in all animals (Table 3). There were main effects for strain ($F_{1,66} = 7.4, P < .01$) and diet ($F_{3,66} = 7.6, P < .01$) in ING and MES (strain: $F_{1,65} = 9.7, P < .01$; diet: $F_{3,65} = 7.3, P < .01$). In comparison to A/J mice, B/6J mice fed the LL diet had lower LPL activity in ING and MES fat ($P < .05$). There was no interaction between strain and diet for LPL activity in ING or MES fat. No main effect of sucrose on ING or MES LPL activity was found in A/J or B/6J mice. No interactions between strain and diet or main effects of strain or diet were found for basal or norepinephrine-stimulated lipolysis (data not shown).

Fasting glucose and insulin. There were significant main effects for both strain ($F_{1,190} = 106.4, P < .0001$) and diet ($F_{3,190} = 27.2, P < .0001$), as well as an interaction between strain and diet, in fasting plasma glucose levels ($F_{3,190} = 13.1, P < .001$). As listed in Table 3, diet did not affect plasma glucose levels in A/J mice. However, in B/6J mice, fat but not sucrose caused an elevation in plasma glucose. Similar results were found for fasting plasma insulin. Main effects were found for both strain ($F_{1,187} = 55.0, P < .0001$) and diet ($F_{3,187} = 20.9, P < .0001$), as well as an interaction of strain and diet ($F_{3,187} = 11.94, P < .001$), in fasting insulin. Whereas diet had no effect on insulin levels of A/J mice, high-fat diets increased insulin levels of B/6J mice. Sucrose had no effect on fasting insulin in either strain. As previously reported,[4] hyperglycemia appeared after 1 month on the diabetogenic diets, whereas hyperinsulinemia was not fully apparent until after 4 months.

Corticosterone. There were no differences in basal corticosterone between strains or diets and no interaction between strain and diet. Stress corticosterone levels were higher in A/J than in B/6J mice ($F_{1,66} = 6.5, P < .02$), and there was a strain x diet interaction ($F_{3,66} = 2.9, P < .05$).

Table 3. Plasma Glucose and Insulin Levels and LPL Activity of A/J and B/6J Mice by Diet Groups

Strain	Plasma Glucose (mg/dL)	Plasma Insulin (µU/mL)	LPL Activity (U per 10^6 cells) ING	LPL Activity (U per 10^6 cells) MES
A/J				
HH	143 ± 4	30.17 ± 3.27	1.405 ± 0.244	1.801 ± 0.305
HL	140 ± 5	27.04 ± 3.38	1.420 ± 0.294	1.373 ± 0.258
LH	134 ± 3	21.18 ± 2.14	0.945 ± 0.148	1.230 ± 0.239
LL	134 ± 3	35.11 ± 4.48	0.894 ± 0.187	0.964 ± 0.157
B/6J				
HH	199 ± 5	134.00 ± 16.42	1.282 ± 0.187	1.337 ± 0.170
HL	183 ± 4	115.92 ± 17.17	0.949 ± 0.149	1.057 ± 0.220
LH	144 ± 4	31.44 ± 3.79	0.572 ± 0.048	0.847 ± 0.135
LL	150 ± 5	43.51 ± 7.80	0.508 ± 0.099	0.488 ± 0.081

NOTE. Results are the mean ± SEM. Significance levels are shown in text.

Experiment II

Caloric intake was greater in animals on the LL diet with sucrose supplementation than in those given plain water ($F_{1,36} = 27.1$, $P < .0001$). Body weight of B/6J mice was greater than that of A/J mice ($F_{1,36} = 32.8$, $P < .0001$). For FE, there was a main effect for strain ($F_{1,36} = 18.8$, $P = .0001$) and for diet ($F_{1,36} = 16.9$, $P = .0002$). This indicates that although A/J mice showed lower FEs than B/6J mice, addition of sucrose to this low-fat diet reduced FE for all animals (Fig 5).

DISCUSSION

Results of this study clearly show that the development of obesity and hyperglycemia in this animal model is a complex interaction of genetic background and diet. As we have previously shown, B/6J mice are differentially susceptible to dietary manipulations and are therefore arguably a better model of human disease than rodents that develop diabetes and obesity spontaneously on standard laboratory chow. It is now apparent that fat, not sucrose, is responsible for the development of diabetes and obesity in this B/6J strain.

The B/6J mouse demonstrates an increased FE (weight gain divided by caloric consumption) for fat. This means that it is able to store more fat than an A/J mouse without consuming more calories. Such a "thrifty genotype" has been postulated to be of adaptive value in conditions of uncertain food supply,[29] but is responsible for pathology when high-fat diets are plentiful. Although the mechanism for this effect is not yet understood, this phenomenon appears to be related to the development of adipocyte hyperplasia. Increased weight in A/J mice on high-fat diets is mainly due to adipocyte hypertrophy, and B/6J mice respond to fat with adipocyte hyperplasia as well. As previously observed,[6] this hyperplasia is most apparent in MES fat, although it occurs to a lesser extent in ING tissue as well. Although fat is known to induce a preferential accumulation of abdominal fat in rodents,[28,30] this effect was only observed in B/6J mice and is therefore apparently genetically determined.

These observations support the notion that fat is important in the development of obesity. In addition, they clearly show that across these two strains of mice, genetic differences in the ability to store fat are more important in the development of obesity than the increase in caloric content of a high-fat diet. Flatt[11] has argued that because the rate of carbohydrate and protein oxidation is determined by intake of these nutrients, whereas the rate of fat oxidation is determined largely by the gap between total energy expenditure and energy intake, obesity is the natural result of a diet rich in fat. He also postulated that high-fat diets may also promote hyperphagia because they may cause a relative glycogen deficiency. Although all animals fed high-fat diets consumed more calories than animals fed low-fat diets, B/6J mice became much more obese than A/J mice without consuming more calories than A/J mice. Since a strain difference in FE was only found in high-fat diets, it is unlikely that this is due to a difference in carbohydrate-stimulated thermogenesis. Our data clearly show that major genetic differences exist in how fat is handled in inbred strains.

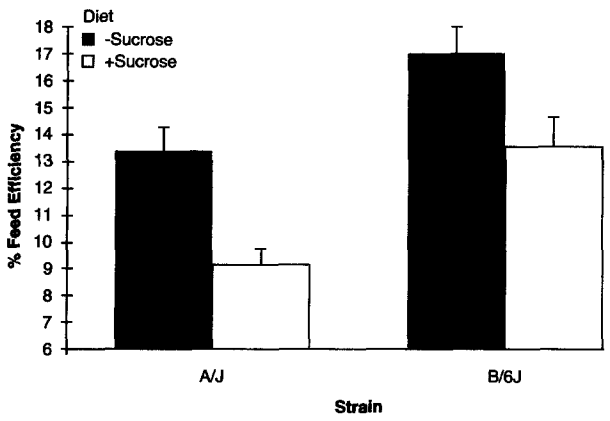

Fig 5. FE of A/J and B/6J mice (± SEM) on LL diets with and without 16% sucrose added to the drinking water.

It has also been postulated that whereas carbohydrate stimulates sympathetic nervous system activity and thermogenesis, fat inhibits this effect by stimulating corticosteroid activity and thereby decreasing hypothalamic corticotropin-releasing factor release.[12] High-fat diets would therefore be predicted to promote hyperphagia by decreasing sympathetic nervous system activity. However, in our study, there were no differences in fat-induced changes in food consumption or basal corticosterone levels between strains, and obesity-resistant mice had higher stress corticosterone levels than obesity-prone mice. Thus, our results cannot be explained in terms of differential effects of fat on corticosteroid activity.

We found that fat was also the primary nutritional stimulus for the development of hyperglycemia and hyperinsulinemia in the B/6J mouse. Sucrose, by comparison, had no effect on blood glucose or insulin in the absence of fat. Fat has been shown to induce hyperglycemia in rats whose pancreatic function has been compromised by streptozocin[15] and in rats supported with a fat-based parenteral infusion over 48 hours.[31] We have recently determined that the B/6J mouse has a defect in glucose-stimulated insulin release. Furthermore, this defect is exacerbated by fat in the diet (manuscript in preparation). Although the mechanism by which fat further compromises pancreatic function and produces hyperglycemia in B/6J mice is yet to be determined, preliminary data suggest that B/6J mice raised on the high-fat diet have increased blood levels of peroxides, as well as decreased blood levels of glutathione (data not shown). Interestingly, it has been previously reported that the B/6J mouse has a deficiency in blood glutathione with increasing age.[32] Thus, B/6J mice may be particularly vulnerable to the deleterious effects of fatty acid oxidation, as described by Opara and Hubbard.[16] It is of particular interest that the fat-induced hyperplasia of adipocytes that occurs in the B/6J mouse is most apparent in the MES fat pad. Studies in humans have shown that both obesity per se and fat distribution seem to be risk factors for type II

diabetes.[33] This suggests that both total fat and fat distribution might be important in the development of diabetes.

Although the amount of sucrose in the HH diet was less than that in the LH diet (due to the caloric density of fat), it is apparent that sucrose has different effects depending on the amount of fat in the diet. When added to the chow without fat, sucrose appeared to have an effect opposite to that of fat on adipocyte size. In the absence of fat, sucrose decreased the size of MES and ING fat pads and MES and ING cell size in B/6J mice. A similar but nonsignificant effect was noted in A/J mice. When sucrose was administered via drinking water, sucrose (again in the absence of fat) decreased FE in both strains. There are several potential mechanisms by which sucrose could induce a decrease in fat mass. Sucrose has been shown to prevent the decreases in resting metabolic rate and triiodothyronine levels in humans that normally occur with caloric restriction.[34] It is possible that high-sucrose feeding could have a stimulatory effect in ad libitum administration. Furthermore, sucrose and glucose are known to be potent stimuli for sympathetic nervous system activity.[35] Thus, it is possible that high-sucrose diets induced an increase in thermogenesis in brown adipose tissue. Because animals that consumed sucrose via drinking water took in less solid food, their consumption of protein decreased by approximately 30%. Because body composition analysis was not performed on these animals, we cannot know for sure whether the weight differences observed were due to decreased lean or fat mass. However, when animals were fed the solid high-sucrose diet (LH), protein intake was the same but FE was still lower.

In summary, this study shows that B/6J mice carry a genetic trait that predisposes them to store fat when dietary fat content is high. In addition, high-fat diets promote the development of hyperglycemia and hyperinsulinemia in this strain. In that diabetes and obesity, induced by a combination of fat and sucrose in the diet, are known to be caused by different genetic factors in B/6J mice,[5,10] it is likely that different genetic variables are responsible for the development of obesity and diabetes in response to fat alone. Thus, the thrifty genotype postulated by Neel[29] may be more related to obesity than to hyperglycemia. This would make sense in that fat storage has an obvious adaptive value. Our study also shows that genetic predisposition can be more important in determining the degree of obesity in response to a high-fat diet than caloric intake. In the B/6J mouse, it must be considered a pathologic response to fat in the diet. If these results are generalizable to human populations, severe obesity will probably not be treated effectively until this pathology is adequately addressed.

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