

Dietary obesity in nine inbred mouse strains

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West, David B., Carol N. Boozer, Deborah L. Moody, and Richard L. Atkinson. Dietary obesity in nine inbred mouse strains. *Am. J. Physiol.* 262 (Regulatory Integrative Comp. Physiol. 31): R1025-R1032, 1992.—The effect of 7 wk consumption of a diet containing 32.6% of kilocalories as fat [condensed milk (CM) diet] on body composition and energy intake was evaluated in nine strains of inbred mice (AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, C57BL/6J, SJL/J, I/STN, and SWR/J). Control animals were fed a high-carbohydrate diet containing 11.6% of energy as fat (Purina Rodent Chow diet). Relative to Chow diet controls, the CM diet significantly increased carcass lipid content in six strains (AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, and C57BL/6J), but had no or a marginal effect on adiposity in three strains of mice (SJL/J, I/STN, and SWR/J). The obesity produced by the CM diet in six strains was not due to hyperphagia. Only one of six (AKR/J) of the strains that increased adiposity on the CM diet consumed more energy than controls during the 7 wk of the experiment. The identification of inbred mouse strains that are sensitive to dietary obesity, vs. others that are resistant, provides a useful tool to pursue the metabolic and genetic basis of this trait in the mouse.

mice; body composition

CONSIDERABLE EVIDENCE indicates that human obesity has a strong genetic component (16). It is likely that some genes responsible for the expression of obesity in an individual operate only under permissive environmental conditions. A clear example of this is the high incidence of obesity now found in the Pima Indians (12). This Indian tribe in the southwest American desert was not obese before the introduction of western European diet and culture. Animal models also exist in which environmental conditions allow the expression of a latent tendency for obesity (7, 8).

One environmental factor that may permit the expression of obesity in humans with a genetic predisposition toward obesity is dietary fat content. Several studies suggest that the proportion of fat in the diet may be an important environmental factor associated with the expression of human obesity (2, 13). Obesity in rodents and other species fed a high-fat diet is also readily observed in the laboratory. Some strains of rats will become obese on a high-fat diet, while others remain lean (14). Similarly, in humans there may exist a variable sensitivity to obesity induced by consuming a diet high in fat energy. A polygenic threshold model of obesity, in which genes interact with environment, has been previously suggested by Festing (5). One key environmental factor influencing the expression of obesity in this model is diet. The specific genes that are responsible for determining sensitivity to dietary obesity are not known. Inbred strains of mice are an ideal tool for elaborating the genetic basis of specific traits and diseases using classical genetic approaches. As a first step to using inbred mice to investigate the genetics of sensi-

tivity to dietary obesity, we have characterized the response of nine strains of mice to a diet high in fat content.

METHODS

Adult male mice from nine different inbred strains were used in this experiment. Eight strains of mice (10 mice/strain) were purchased at 4 wk of age from Jackson Laboratories (Bar Harbor, ME). These strains included the AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, C57BL/6J, SJL/J, and SWR/J strains. Ten male I/STN mice were obtained from the Roswell Park Memorial Institute (Buffalo, NY) at 6–10 wk of age. After arrival, the mice were individually housed and maintained ad libitum on Purina Rodent Chow (no. 5001, Ralston Purina, St. Louis, MO) and water for 1 wk. Mice were then randomly assigned to condensed milk (CM) or Chow diets, with five animals of each strain assigned to each dietary condition. For all strains except the SWR/J strain the number of animals in the Chow and CM diet conditions was five. For the SWR/J strain there were five animals fed the CM diet and four animals fed the Chow diet because of the loss of one animal. The pelleted CM diet was composed by weight of 44% sweetened condensed milk, 47% Purina Rodent Chow (no. 5001), 8% corn oil, and 1% corn starch (diet no. C11024, Research Diets, New Brunswick, NJ). The CM diet contained 32.6, 15.0, and 52.4% of kilocalories as fat, protein, and carbohydrate, respectively. The use of the CM diet was based on the observation by Levin et al. (10) that a similar diet fed to Sprague-Dawley rats produced obesity in some but not all animals. Animals assigned to the Chow diet were continuously maintained on Purina Rodent Chow (no. 5001). The Chow diet contained 11.6, 26.4, and 62.0% of kilocalories as fat, protein, and carbohydrate, respectively.

Mice were fed the diets for 7 wk. Beginning 1 wk before assigning the animals to their specific dietary condition (*week 0*) until the end of the experiment, the mice were weighed on Monday, Wednesday, and Friday of each week. Daily diet intake was determined by weighing the food remaining in each cage on Monday, Wednesday, and Friday and replacing it with fresh preweighed diet. Diet intake was calculated by subtracting the weight of the uneaten diet from the preweighed amount added to the cage. Spillage of diet was not measured. Energy intakes were calculated on the basis of 3.5 kcal/g of Chow diet and 4.5 kcal/g of CM diet. These energy values were calculated from the macronutrient composition using values of 4, 4, and 9 kcal/g of carbohydrate, protein, and fat, respectively.

After 7 wk of feeding, the mice were decapitated using surgical scissors after stunning by cervical dislocation. Inguinal, retroperitoneal, epididymal, mesenteric, and interscapular brown adipose depots, as well as liver, were removed and weighed. No other adipose depots were removed. The eviscerated carcass, with liver and adipose depots removed, was homogenized using a polytron homogenizer (Brinkman Polytron PT6000 with 1.25-in. head) in distilled water and its composition determined. Samples of carcass homogenate were dried to a constant weight in an oven at 55°C to determine carcass water content. Lipid was measured by the method of Folch (6). Adipose depot lipid content was determined separately for the combined depots and the weight of lipid in the depots added to the eviscerated carcass lipid content to derive total carcass lipid content. Carcass ash

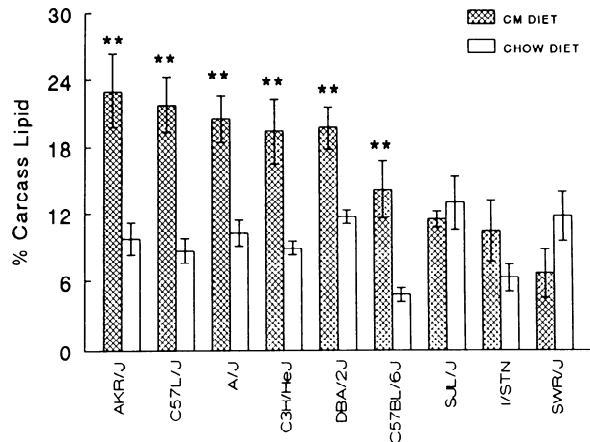


Fig. 1. Percent of carcass composed of lipid in mice from 9 inbred strains fed either condensed milk (CM) diet or Purina Rodent Chow diet. Data are presented as mean values, with error bars representing SE. ** $P < 0.01$, significant CM diet vs. Chow diet difference within a strain (ANOVA and Tukey's protected t test).

was measured by ashing samples of carcass homogenate in a Thermolyne ashing furnace (model F-A2025P) at 600°C for 4 h according to the protocol recommended for that instrument by the manufacturer. Lean body tissue weight was calculated by

subtracting water and lipid weight from the total carcass weight. After decapitation, truncal blood was collected over heparin. Plasma was obtained by centrifuging the blood for 2 min at 12,000 revolutions/min using an Eppendorf microcentrifuge. The plasma was frozen at -70°C and later assayed for glucose with a YSI glucose analyzer (model 27, Yellow Springs Instruments, Yellow Springs, OH).

The data were analyzed by a two-way (diet $\times$ strain) analysis of variance (ANOVA) for most variables. If a significant ($P < 0.05$) main effect of diet was observed, the statistical difference between CM diet and Chow diet animals within each strain was assessed with Tukey's protected t test.

RESULTS

Body composition. Analysis of carcass lipid content (Fig. 1, Table 1) indicates that some strains significantly increased total body adiposity when fed the CM diet (6 of 9 strains: AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, and C57BL/6J). Other strains (3 of 9 strains: I/STN, SWR/J, and SJL/J) did not increase adiposity with the CM diet (%carcass lipid: $F_{1,8} = 55.95$, $P < 0.0001$). These changes of body fat content, expressed either as a percentage of carcass weight or as absolute total carcass lipid, are also reflected in the increased weight of dissected adipose depots (Table 2). In the same six strains that increased total carcass lipid on the CM diet, the epididymal, retroperitoneal, and inguinal adipose depot weights were sig-

Table 1. Carcass composition

Strain	Diet	Weight, g					%Lipid	%Water	%Ash	%Lean Tissue
		Total carcass	Lipid	Water	Ash	Lean tissue				
AKR/J	CM	27.45*	6.56*	14.75	0.67	6.14	23.00*	54.56*	2.47	22.44
	Chow	±1.93 21.97	±1.31 2.18	±0.37 14.40	±0.07 0.63	±0.40 5.38	±3.32 9.81	±2.96 65.65	±0.24 2.84	±0.76 24.54
C57L/J	CM	24.95*	5.58*	13.56	0.71	5.81	21.85*	54.74*	2.87	23.41
	Chow	±1.24 19.88	±0.90 1.78	±0.20 12.64	±0.05 0.77	±0.17 5.46	±2.50 8.74	±1.94 63.87	±0.29 3.88	±0.68 27.40
A/J	CM	21.01*	4.38*	12.17*	0.47	4.46	20.50*	58.34	2.24	21.16
	Chow	±1.12 16.22	±0.68 1.69	±0.41 10.29	±0.05 0.48	±0.33 4.25	±2.12 10.32	±2.59 63.41	±0.18 2.99	±0.78 26.27
C3H/HeJ	CM	22.44†	4.54*	12.65	0.65	5.24	19.38*	57.15*	2.89	23.47
	Chow	±1.68 19.04	±0.84 1.73	±0.51 12.50	±0.07 0.50	±0.37 4.81	±2.93 9.02	±2.53 65.68	±0.14 2.58	±0.73 25.29
DBA/2J	CM	20.94†	4.21†	11.78	0.49	4.96	19.71*	56.53†	2.37	23.76
	Chow	±1.11 17.55	±0.63 2.06	±0.37 11.02	±0.08 0.66	±0.27 4.47	±1.86 11.71	±1.77 62.88	±0.38 3.77	±1.02 25.41
C57BL/6J	CM	21.41†	3.11*	13.05	0.55	5.25†	14.24*	61.17*	2.60	24.59
	Chow	±0.56 17.92	±0.67 0.87	±0.11 12.75	±0.06 0.43	±0.10 4.30	±2.63 4.84	±1.90 71.13	±0.33 2.39	±0.81 24.03
SJL/J	CM	18.31	2.12	11.25	0.77	4.95	11.49	61.55	3.77	26.96
	Chow	±0.66 17.48	±0.21 2.30	±0.26 10.78	±0.06 0.69	±0.29 4.39	±0.74 12.96	±1.15 61.96	±0.53 2.57	±0.90 25.08
I/STN	CM	19.34	2.11	12.32	0.52	4.91	10.46	63.95	2.75	25.59
	Chow	±1.06 17.15	±0.63 1.06	±0.51 11.46	±0.07 0.59	±0.13 4.63	±2.71 6.27	±1.83 66.75	±0.42 3.44	±0.95 26.98
SWR/J	CM	18.73	1.30	12.58	0.44	4.84*	6.77	67.29	2.35	25.94
	Chow	±0.67 17.46	±0.31 2.09	±0.33 11.71	±0.07 0.34	±0.13 3.66	±1.43 11.84	±0.94 67.19	±0.32 1.95	±0.70 20.97
		±0.52	±0.44	±0.15	±0.15	±0.32	±2.23	±1.49	±0.84	±1.77

Values are means $\pm$ SE. Lean tissue mass is defined as carcass mass minus lipid and water mass. Each variable was analyzed by a 2-way (diet $\times$ strain) ANOVA. If there was a significant main effect of diet, differences between diet groups within each strain were evaluated by Tukey protected t test. * $P < 0.01$; † $P < 0.05$, significant condensed milk (CM) vs. Chow diet difference within a strain.

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Table 2. Weight of adipose depots and liver

Strain	Diet	Weight, g					
		Epididymal depot	Retroperitoneal depot	Inguinal depot	Mesenteric depot	Interscapular brown adipose depot	Liver
AKR/J	CM	1.50±0.34*	0.39±0.07*	0.90±0.22	0.51±0.11*	0.12±0.02†	1.35±0.07
	Chow	0.44±0.09	0.10±0.03	0.33±0.05	0.25±0.04	0.07±0.00	1.39±0.06
C57L/J	CM	0.86±0.11*	0.30±0.07*	0.73±0.12*	0.42±0.09*	0.15±0.02†	1.07±0.05
	Chow	0.32±0.07	0.04±0.02	0.21±0.05	0.14±0.03	0.10±0.01	1.02±0.08
A/J	CM	0.63±0.09†	0.20±0.05*	0.94±0.16*	0.38±0.05*	0.08±0.01	0.89±0.05
	Chow	0.21±0.04	0.05±0.01	0.34±0.05	0.20±0.03	0.06±0.01	0.84±0.04
C3H/HeJ	CM	0.81±0.18*	0.23±0.05*	0.70±0.14*	0.35±0.05	0.18±0.02*	1.02±0.05
	Chow	0.21±0.03	0.06±0.01	0.26±0.03	0.22±0.02	0.10±0.01	1.16±0.02
DBA/2J	CM	0.75±0.11†	0.20±0.03†	0.60±0.09†	0.35±0.05	0.16±0.02*	1.05±0.05
	Chow	0.35±0.03	0.08±0.01	0.30±0.02	0.26±0.01	0.09±0.01	1.09±0.03
C57BL/6J	CM	0.61±0.13†	0.17±0.05*	0.48±0.13†	0.19±0.04	0.09±0.01	0.99±0.02
	Chow	0.16±0.03	0.07±0.01	0.14±0.02	0.08±0.01	0.06±0.01	1.03±0.05
SJL/J	CM	0.51±0.06	0.11±0.02	0.32±0.03	0.15±0.02	0.08±0.01	1.02±0.05
	Chow	0.42±0.11	0.10±0.05	0.36±0.09	0.12±0.02	0.09±0.01	1.03±0.04
I/STN	CM	0.34±0.14	0.10±0.04	0.25±0.07	0.19±0.05	0.07±0.01	1.00±0.08
	Chow	0.12±0.03	0.04±0.01	0.16±0.02	0.17±0.02	0.04±0.01	1.07±0.05
SWR/J	CM	0.20±0.06	0.04±0.02	0.21±0.05	0.16±0.03	0.07±0.01	1.06±0.05
	Chow	0.30±0.08	0.08±0.04	0.38±0.14	0.21±0.04	0.08±0.01	1.08±0.04

Values are means ± SE. Each variable was analyzed by a 2-way (diet × strain) ANOVA. If there was a significant main effect of diet, differences between diet groups within each strain were evaluated by Tukey's protected *t* test. **P* < 0.01; †*P* < 0.05, significant CM vs. Chow diet difference within a strain.

nificantly increased relative to same strain animals fed the Chow diet (inguinal $F_{1,8} = 39.40$, $P < 0.0001$; retroperitoneal $F_{1,8} = 4.784$, $P < 0.001$; epididymal $F_{1,8} = 50.62$, $P < 0.0001$). In the three strains that showed no significant increase in total carcass lipid with the CM diet, there was no increase in adipose depot weight. Mesenteric depot weight increased with CM diet feeding in three of six strains that were responsive and zero of three strains that were nonresponsive to CM diet feeding ($F_{1,8} = 27.31$, $P < 0.0001$). Similarly, interscapular brown adipose tissue weight increased in four of six responsive strains and zero of three nonresponsive strains ($F_{1,8} = 10.401$, $P < 0.0001$).

Total carcass water and lean body tissue (lipid- and water-free carcass) weight were generally increased by the CM diet, while carcass ash weight was not affected (Table 1) (carcass water $F_{1,8} = 14.80$, $P < 0.0001$; lean body tissue $F_{1,8} = 19.53$, $P < 0.0001$; ash $F_{1,8} = 0.816$, $P < 0.369$). The percent of the carcass composed of water was decreased by CM diet in five of six responsive strains and zero of three of the nonresponsive strains ($F_{1,8} = 41.53$, $P < 0.001$). The CM diet did not affect the percentage of the carcass composed of lean body tissue ($F_{1,8} = 3.44$, $P < 0.07$) or ash ($F_{1,8} = 1.11$, $P < 0.29$). Liver weight was not affected by the CM diet in any strain (Table 2).

Body weight. Immediately before the start of CM diet feeding (week 0), there were no significant differences in body weight between the animals assigned to the Chow diet vs. the CM diet condition within any strain (Table 3). However, there were significant interstrain differences in body weight at week 0 ($F_{1,8} = 73.61$, $P < 0.0001$). The AKR/J mice were the heaviest, while the DBA/2J mice were the lightest. The SWR/J mice (one of the non-responsive strains) were intermediate in body weight.

After the start of the CM diet (week 1), there was a clear tendency for the animals fed the CM diet to diverge in body weight from the animals fed the Chow diet. By week 7 of CM diet feeding, four of the nine strains showed a significant difference in body weight between the

groups fed the CM and Chow diets ($F_{1,8} = 29.46$, $P < 0.0001$). In seven of nine strains, the animals fed the CM diet gained significantly more weight than the controls fed the Chow diet over the 7 wk of the experiment ($F_{1,8} = 61.13$, $P < 0.0001$). The differential effect of the CM diet on body weight among the different strains is illustrated in Fig. 2. In some strains (e.g., AKR/J, A/J, and C57BL/6J) the animals fed the CM diet gained progressively more weight compared with animals fed the Chow diet. In other strains (e.g., I/STN, SWR/J, and SJL/J) the mice fed the CM diet gained only slightly more weight over the 7-wk period compared with mice fed the Chow diet.

Energy intake. Cumulative intake of energy over the 7 wk of the experiment was not related to the change in adiposity induced by the CM diet in the different strains (Fig. 3). In two of the three strains that did not show a significant increase of adiposity with CM diet feeding, the animals fed the CM diet still consumed significantly more energy over the 7 wk of the study compared with controls fed the Chow diet ($F_{1,8} = 12.05$, $P < 0.0009$). The CM diet significantly affected cumulative energy intake in only two of six responsive mouse strains. In one of these strains (AKR/J), cumulative intake was increased in the group fed the CM diet; while in another strain (C57L/J), the animals fed the CM diet consumed significantly fewer kilocalories than Chow diet animals.

When energy intake was expressed per gram of body weight (Table 4), a clear trend was evident. During the first week of access to the CM diet, the CM diet group in most strains consumed significantly more energy per gram of body weight than the Chow diet group (5 of 9 strains). This was the trend observed in the six responsive strains as well as the three strains that did not increase adiposity with feeding the CM diet. After this generalized hyperphagia during the first week, animals fed the CM diet quickly returned to an energy intake (expressed per g body wt) that was not different from mice fed the Chow diet. By the fifth week of dietary manipulation, animals consuming the CM diet in four of

Table 3. *Body weight*

Strain	Diet	Week								Change Week 7 – Week 0
		0	1	2	3	4	5	6	7	
AKR/J	CM	22.72 ±0.81	26.59 ±0.89	28.84 ±0.99	30.12 ±1.09	32.50 ±1.29	34.49 ±1.71	35.42† ±2.06	36.02* ±2.26	13.28* ±1.63
	Chow	22.64 ±0.45	25.71 ±1.00	27.53 ±1.24	28.07 ±1.07	29.79 ±1.06	31.11 ±1.02	31.65 ±1.21	31.25 ±0.90	8.06 ±0.53
C57L/J	CM	21.04 ±0.92	23.62 ±0.75	24.26 ±0.72	25.59 ±0.67	26.68 ±0.70	28.18 ±0.95	30.05 ±1.03	31.87† ±1.36	11.26* ±0.58
	Chow	20.44 ±1.57	22.60 ±1.62	23.54 ±1.62	24.53 ±1.64	25.23 ±1.59	26.38 ±1.48	27.35 ±1.48	28.10 ±1.62	7.96 ±0.37
A/J	CM	15.82 ±1.17	19.24 ±1.07	20.98 ±1.15	22.27 ±1.08	23.46† ±1.08	24.65† ±1.19	25.82† ±1.15	26.74* ±1.26	10.92* ±0.38
	Chow	15.42 ±1.06	17.87 ±0.84	19.09 ±0.81	19.64 ±0.87	20.56 ±0.90	21.51 ±0.80	22.54 ±0.64	22.46 ±0.83	6.68 ±0.95
C3H/HeJ	CM	17.52 ±0.91	21.67 ±1.00	23.47 ±1.25	25.03 ±1.41	26.23 ±1.28	26.62 ±1.48	27.73 ±1.57	28.34 ±1.81	10.82† ±1.10
	Chow	17.70 ±0.86	20.60 ±1.04	22.22 ±1.03	23.29 ±0.97	24.11 ±0.77	24.70 ±0.82	25.61 ±0.90	25.86 ±0.99	8.16 ±0.54
DBA/2J	CM	15.30 ±1.04	18.31 ±1.00	20.83 ±0.82	23.39 ±0.84	25.85† ±0.84	26.95 ±1.13	27.83† ±1.20	28.06 ±1.33	12.76† ±0.75
	Chow	15.26 ±0.71	17.41 ±0.50	19.85 ±0.59	21.27 ±0.75	22.97 ±0.66	24.19 ±0.69	24.67 ±0.65	25.38 ±0.50	10.12 ±0.63
C57BL/6J	CM	17.86 ±0.49	21.07 ±0.35	22.66† ±0.40	23.97† ±0.38	24.90† ±0.45	25.85 ±0.44	26.94† ±0.46	28.38† ±0.53	11.06* ±2.42
	Chow	17.18 ±0.54	18.95 ±0.45	20.38 ±0.50	21.52 ±0.48	22.54 ±0.45	23.57 ±0.47	24.30 ±0.47	25.28 ±0.38	8.43 ±0.66
SJL/J	CM	19.86 ±0.68	21.53 ±0.79	22.66 ±0.82	23.45 ±0.77	23.89 ±0.64	24.51 ±0.77	25.34 ±0.70	25.79 ±0.64	6.22 ±0.30
	Chow	19.72 ±0.68	20.85 ±0.72	21.79 ±0.65	22.58 ±0.75	23.54 ±0.82	24.03 ±0.79	24.85 ±0.99	25.58 ±0.86	6.30 ±0.45
I/STN	CM	21.80 ±1.09	23.38 ±1.27	23.95 ±1.06	24.83 ±1.11	25.65 ±1.16	26.39 ±1.19	26.07 ±1.08	26.68 ±1.20	5.12† ±0.73
	Chow	22.08 ±0.94	22.25 ±0.80	22.81 ±0.66	23.59 ±0.57	24.18 ±0.60	24.70 ±0.59	24.36 ±0.38	24.85 ±0.44	2.70 ±0.52
SWR/J	CM	17.90 ±1.22	20.37 ±1.06	21.99 ±1.25	22.91 ±0.92	24.39 ±0.66	25.56 ±0.69	25.84 ±0.78	25.84 ±0.78	7.94 ±0.80
	Chow	18.15 ±0.64	19.69 ±0.42	21.16 ±0.16	21.44 ±0.32	22.74 ±0.41	23.76 ±0.33	24.68 ±0.27	24.36 ±0.33	6.23 ±0.65

Values are in grams and are means ± SE. Each variable was analyzed by a 2-way (diet × strain) ANOVA. If there was a significant main effect of diet, differences between diet groups within each strain were evaluated by Tukey's protected *t* test. **P* < 0.01; †*P* < 0.05, significant CM vs. Chow diet difference within a strain.

six responsive strains were actually consuming less energy than controls fed the Chow, while in the nonresponsive strains the animals fed the CM diet were consuming the same number of kilocalories per gram of body weight as the controls fed the Chow diet (Table 4).

This different pattern of energy intake of the CM diet across the 7 wk of the experiment in responsive and nonresponsive strains is highlighted in Fig. 4. The data from the six responsive strains were combined and energy intake of Chow and CM diet expressed weekly across the 7 wk of the experiment. Similarly, the data from the three nonresponsive strains were combined and analyzed. A clear difference in the pattern of intake is obvious. In both the responsive and nonresponsive strains, energy intake of the CM and Chow diet diminishes with age. However, in the responsive strains, the intake of CM diet is actually less than that of Chow diet during the last 3 wk of the experiment. In the nonresponsive strains, the energy intake of the CM diet remains higher than the intake of Chow diet for the entire experiment (3-way ANOVA, diet × response group × week: $F_{1,16} = 30.72$, $P < 0.0001$; diet by group interaction).

Energy intake during the last week of the study (week 7) was also expressed per gram of lean body tissue (i.e., per gram of lipid- and water-free carcass) (Fig. 5). Overall, animals fed the CM diet consumed significantly fewer

kilocalories than animals fed the Chow diet when intake was expressed per gram of lean body tissue ($F_{1,8} = 3.86$, $P < 0.05$). Pairwise comparisons between mice fed the Chow diet and CM diet within a strain indicated that this difference was statistically reliable in only one strain (C57BL/6J).

Feed efficiency (defined as g body wt gained/100 kcal diet consumed) was significantly higher in animals fed the CM diet in five of six responsive strains, but was elevated by the CM diet in only one of three of the nonresponsive strains (Fig. 6) ($F_{1,8} = 49.94$, $P < 0.0001$).

Plasma glucose. Although there were significant differences among strains in fasting plasma glucose (Fig. 7), there was no significant effect of feeding the CM diet on glucose concentration ($F_{1,8} = 1.96$, $P < 0.17$).

DISCUSSION

Feeding a condensed milk diet to mice for 7 wk clearly produced a marked increase in body lipid content in the majority of strains tested. Six of nine strains significantly increased adiposity with CM diet feeding: AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, and C57BL/6J. The most responsive was the AKR/J strain, which had the highest percentage of carcass lipid when fed the CM diet. Three strains did not significantly increase body adiposity with CM diet feeding: SJL/J, I/STN, and SWR/J.

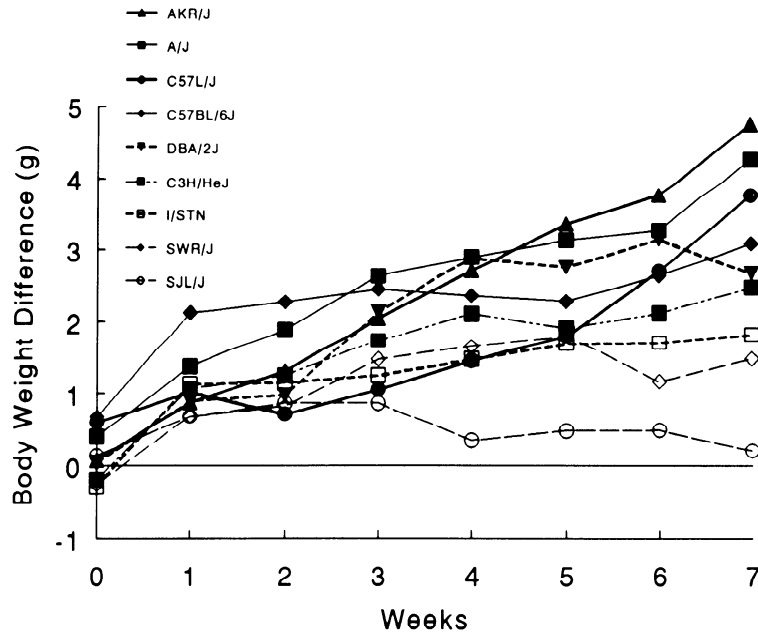


Fig. 2. Difference in body weight in grams between animals fed either CM diet or Chow diet for each of 9 inbred strains across the 7 wk of the experiment. Numbers were calculated by subtracting mean weight (g) of Chow diet group during each week from mean weight of CM diet group for each strain.

Although the I/STN animals increased mean carcass lipid content by ~50% in the group fed the CM diet compared with controls fed the Chow diet, this increase was not statistically reliable. Fenton and Carr (4) previously reported that the I strain was resistant to dietary obesity. This resistance to dietary obesity has been attributed to a decreased proliferative capacity of preadipocytes in the I mouse (3). Our results suggest that with the CM-based diet the I/STN mice may in fact respond by increasing adiposity. However, the ability of the I/STN mice to increase adiposity on this diet is certainly reduced compared with the responsive strains, which generally increased adiposity by >100% when fed the CM diet.

Two strains of mice (SJL/J and SWR/J) did not

increase adiposity with CM diet feeding. In fact, the SWR/J strain actually decreased adiposity slightly with the CM diet. Adiposity of these two nonresponsive strains fed the Chow diet is comparable to the adiposity of the responsive strains fed the Chow diet. Therefore, a generalized developmental defect in adipose tissue growth is not a likely explanation for the failure to increase adiposity with CM diet feeding in these two nonresponsive strains.

Initial body weight was not a predictor of responsiveness to CM diet feeding. At 5 wk of age the nonresponsive strains were not significantly smaller in total body weight compared with several of the responsive strains. Similarly, the body weight of the nonresponsive strains after 7 wk of Chow diet feeding was comparable to that of several of the responsive strains. Additionally, the weight gain of two of the nonresponsive strains (SWR/J and SJL/J) on the Chow diet was not significantly less than five of six of the responsive strains. Thus an overall stunting of growth does not explain the failure to increase adiposity with CM diet feeding in the SJL/J or SWR/J strains. However, a generalized stunting of growth may be a factor in the inability of the I/STN mouse to increase adiposity on the CM diet.

The increase of body weight with CM diet feeding in the responsive strains was primarily due to an increase in body lipid content. However, there was also an overall effect of the CM diet to increase lean body tissue and body water content. CM diet feeding had no consistent effect on carcass ash content, indicating that the diet neither stimulated nor inhibited skeletal growth. These changes in carcass composition with CM diet feeding in the mouse are similar to the changes in rats induced by feeding a high-fat diet (9, 15).

The increased carcass lipid content in the responsive strains fed the CM diet resulted in approximately equivalent and proportional increases in weight of the epididym-

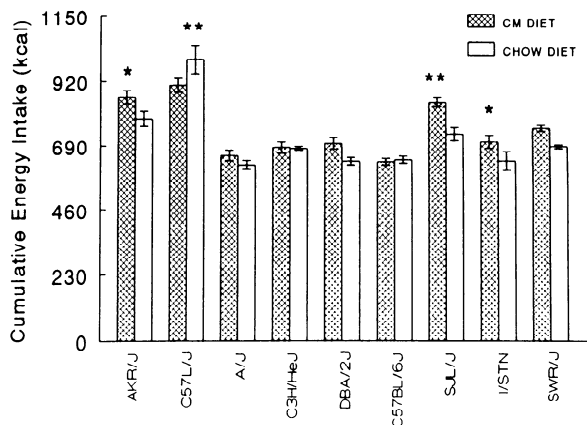


Fig. 3. Cumulative energy intake of 9 strains of inbred mice during 7 wk of feeding a CM diet or Chow diet. Data are presented as mean values, with error bars representing SE. * $P < 0.05$; ** $P < 0.01$, significant CM diet vs. Chow diet difference in cumulative intake within a strain (ANOVA and Tukey's protected t test).

Table 4. Kilocalories consumed per gram body weight per day

Strain	Diet	Week						
		1	2	3	4	5	6	7
AKR/J	CM	0.78±0.02†	0.66±0.01	0.60±0.03	0.62±0.02	0.60±0.02	0.55±0.02	0.54±0.01
	Chow	0.69±0.02	0.62±0.01	0.58±0.03	0.62±0.02	0.60±0.01	0.61±0.01	0.60±0.02
C57L/J	CM	1.02±0.04*	0.68±0.01	0.59±0.01	0.56±0.02	0.52±0.01	0.55±0.01	0.50±0.01
	Chow	0.78±0.02	0.71±0.02	0.62±0.01	0.48±0.05	0.47±0.03	0.52±0.01	0.49±0.01
A/J	CM	0.87±0.01†	0.70±0.02	0.63±0.03	0.63±0.02	0.62±0.02	0.59±0.04	0.56±0.02
	Chow	0.77±0.07	0.72±0.06	0.67±0.05	0.72±0.09	0.70±0.03	0.65±0.04	0.64±0.05
C3H/HeJ	CM	0.80±0.01	0.68±0.02	0.58±0.01	0.57±0.02	0.55±0.03	0.59±0.03	0.54±0.06
	Chow	0.74±0.02	0.70±0.02	0.65±0.04	0.64±0.03	0.64±0.02	0.62±0.02	0.58±0.03
DBA/2J	CM	0.86±0.02	0.73±0.04	0.69±0.01	0.63±0.02	0.58±0.02	0.59±0.02	0.52±0.02
	Chow	0.77±0.03	0.72±0.03	0.63±0.03	0.65±0.01	0.64±0.02	0.62±0.02	0.55±0.02
C57BL/6J	CM	0.69±0.01	0.62±0.01	0.58±0.01	0.57±0.01	0.58±0.01	0.56±0.01	0.56±0.00
	Chow	0.72±0.01	0.69±0.02	0.65±0.02	0.66±0.01	0.67±0.01	0.64±0.01	0.62±0.01
SJL/J	CM	1.05±0.04*	0.70±0.01	0.59±0.02	0.58±0.03	0.56±0.02	0.59±0.02	0.58±0.02
	Chow	0.82±0.03	0.66±0.02	0.60±0.02	0.49±0.04	0.47±0.03	0.53±0.01	0.54±0.02
I/STN	CM	0.79±0.02*	0.57±0.03	0.62±0.03	0.58±0.01	0.61±0.02	0.64±0.03	0.77±0.06
	Chow	0.65±0.02	0.60±0.03	0.57±0.03	0.58±0.02	0.60±0.03	0.62±0.02	0.72±0.02
SWR/J	CM	0.86±0.03	0.74±0.05	0.71±0.04	0.71±0.03	0.72±0.03	0.68±0.03	0.73±0.03
	Chow	0.78±0.05	0.69±0.02	0.72±0.02	0.71±0.01	0.69±0.02	0.65±0.01	0.64±0.03

Values are means ± SE. Each week was analyzed by a 2-way (diet × strain) ANOVA. If there was a significant main effect of diet, differences between diet groups within each strain were evaluated by Tukey's protected *t* test. **P* < 0.01; †*P* < 0.05, significant CM vs. Chow diet difference within a strain.

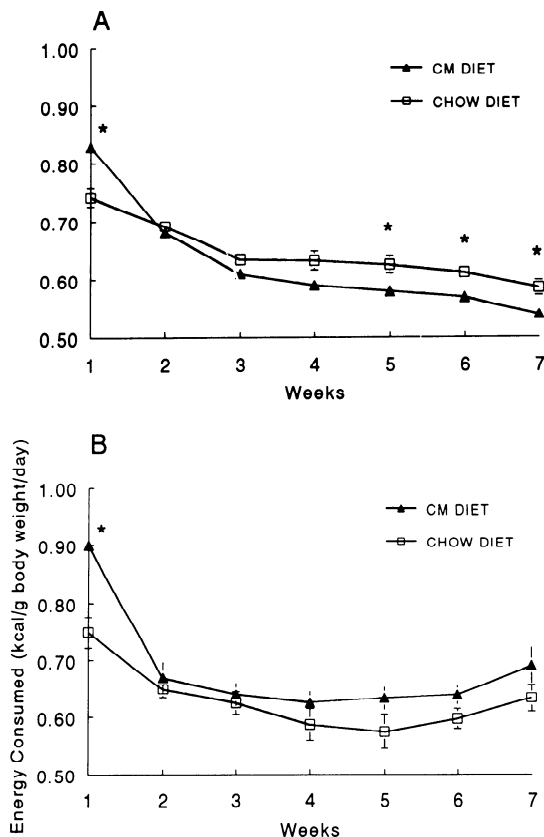


Fig. 4. A: energy intake per gram of body weight per day for responsive strains (AKR/J, C57L/J, A/J, C3H/HeJ, DBA/2J, and C57BL/6J) fed CM diet (*n* = 30) or Chow diet (*n* = 30) for each week of the experiment. B: energy intake for nonresponsive strains (SJL/J, I/STN, and SWR/J) fed CM diet (*n* = 15) or Chow diet (*n* = 14). Data are presented as mean values, with error bars representing SE. Data were analyzed by a 3-way ANOVA (diet × response group × week) followed by Tukey's protected *t* test to assess differences between groups fed CM or Chow diets within responsive and nonresponsive strains. **P* < 0.05, significant CM diet vs. Chow diet difference (ANOVA and Tukey's protected *t* test).

mal, retroperitoneal, and inguinal adipose depots. Mesenteric depot and interscapular brown adipose depot weight were not increased in the same proportion as the other adipose depots by the CM diet. This suggests that these two adipose depots may be of lesser importance for long-term energy storage than the other dissected depots. Liver weight was not affected by CM diet feeding.

The ability of some strains to gain adiposity on the CM diet, while other strains remained lean on the CM diet, was not explained by differences in energy intake. Cumulative energy intake was not increased by the CM diet in five of six responsive strains, while it was significantly increased by the CM diet in two of three nonresponsive strains. One of the responsive strains actually consumed fewer cumulative kilocalories on the CM diet compared with Chow diet controls.

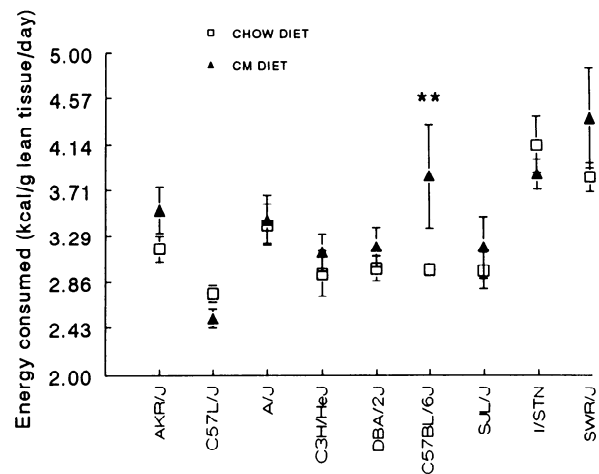


Fig. 5. Energy (kcal) consumed per gram of lean body tissue (i.e., per gram of lipid and water free carcass) per day by mice fed CM diet and mice fed Chow diet from 9 inbred strains during week 7 of the experiment. Data are presented as means, with error bars indicating SE. ***P* < 0.05, significant CM diet vs. Chow diet difference (ANOVA and Tukey's protected *t* test).

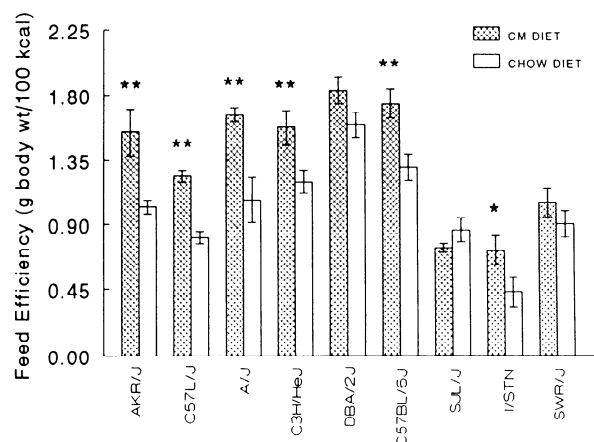


Fig. 6. Feed efficiency (g body wt change/100 kcal consumed) over the 7 wk of the study for animals fed CM diet or Chow diet in 9 inbred strains. Data are presented as mean values, with error bars representing SE. * $P < 0.05$; ** $P < 0.01$, significant CM diet vs. Chow diet difference in feed efficiency within a strain (ANOVA and Tukey's protected t test).

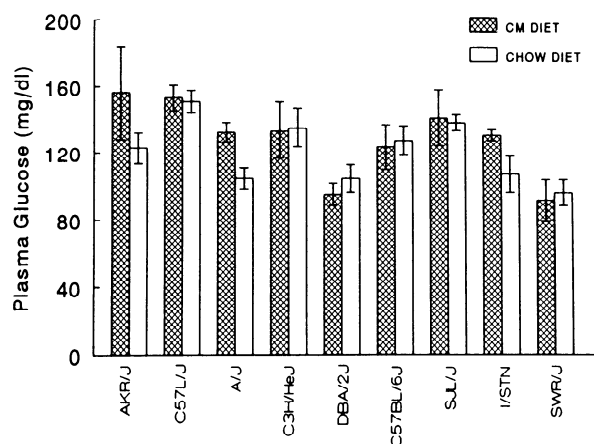


Fig. 7. Plasma glucose (mg/dl) for CM diet- and Chow diet-fed mice from 9 inbred strains.

One can argue that energy intake in responsive animals fed the CM diet was actually decreased relative to Chow diet controls. Although there was a period of hyperphagia in most strains when initially exposed to the CM diet, this hyperphagia was transient and was only observed during the first week of feeding the CM diet. By the seventh week of the dietary manipulation, responsive strains consuming the CM diet were actually consuming fewer kilocalories per gram of body weight, and per gram of lean body tissue, compared with Chow diet controls. This is consistent with the interpretation that, as body adiposity increases, regulatory factors cause a decreased energy intake to limit further increases in adipose lipid stores.

The findings of variable sensitivity to dietary obesity among inbred mouse strains fed the CM-based diet with moderate fat content is consistent with the variable sensitivity within an outbred rat strain fed the identical diet (10). However, in the outbred rat strain, the sensitivity to dietary obesity appears to be related to intake of the diet.

That is, in Sprague-Dawley rats, those animals that are sensitive to dietary obesity consume more of the diet than those that are resistant to the diet. It is not clear whether this relative hyperphagia in the responsive rats is necessary for their increased accumulation of body fat compared with the nonresponsive rats. Cumulative consumption of energy is not a factor determining which mouse strain will become obese on the CM diet.

The small number of mice of each strain used in the present experiment does not allow for any conclusions regarding variable responses to the CM diet within a strain. Because the mouse strains were inbred and genetically homogeneous within a strain, one would expect lesser variability in response than that observed in outbred Sprague-Dawley rats (10). However, stochastic developmental effects or early environmental variables could certainly influence later sensitivity to dietary obesity. Additional studies will be required to determine whether the sensitivity to dietary obesity within an inbred mouse strain is as variable as that observed within outbred rat strains.

The CM diet contained not only significantly more energy from fat compared with the Chow diet, it also contained less energy from protein and it contained simple sugars (sucrose and lactose). It is not clear which dietary factors are responsible for the increased adiposity in responsive mice fed the CM diet. Determination of the specific dietary factors responsible for the increased adiposity in mice fed the CM diet must await the completion of studies examining specific macronutrient manipulations of defined diets. These studies are in progress.

The inability to increase carcass lipid stores when presented with an abundance of food might be maladaptive in a wild animal. The animal that cannot increase carcass energy stores during periods of surplus would be less likely to survive periods of famine. Thus one would expect that the inability to increase adipose lipid stores would be relatively rare. This was the case in the present study in which only two of nine mouse strains showed no tendency to increase adiposity on a CM diet. A similar finding was reported by Schemmel et al. (14) in the rat with only one of seven rat strains not becoming obese on a high-fat diet. The mechanisms responsible for this resistance to dietary obesity are unknown, although it could be due to either genetic or environmental factors. It is unlikely that postweaning environmental factors are an important determinant of this trait, since most of the mouse strains were exposed to an identical environment after weaning. However, differences among the strains in preweaning and in utero environment are possible. It has been reported that the SWR/J mice have smaller pups, and cross-strain embryo transplantation experiments have suggested that the smaller weights of SWR/J pups early in development is due in part to the uterine environment (1). Since manipulations of metabolic state of the dam, as well as nutritional manipulations, have been shown to have persistent effects on the adiposity of the offspring (11), the metabolic status of the mother during pregnancy may be one factor influencing differential sensitivity to dietary obesity among the mouse strains we have examined.

In summary, we have observed that some mouse strains are responsive to dietary obesity when fed a diet contain-

ing moderate levels of fat, while other strains are not responsive and do not become obese when fed the same diet. The obesity induced by feeding the CM diet is generally not attributable to increased consumption of energy. For one of the strains (I/STN), the inability to increase adiposity on the CM diet may be attributable to a defect in proliferative capacity of the adipose tissue. However, in the other two nonresponsive strains, we are not aware of any developmental or metabolic abnormality that accounts for the observed resistance to dietary obesity. The presence of such a robust difference in sensitivity to dietary obesity among several inbred strains of mice will provide a useful tool for identifying the genetic basis of this trait in the mouse.

The gift of the I/STN mice from Dr. Verne Chapman of the Roswell Park Memorial Institute is gratefully acknowledged. We thank Michele Wallace, Carrie Price, and Ahlam Elhady for their technical assistance.

This work was funded by Dept. of Veterans Affairs Merit Review Award 8701 given to R. L. Atkinson and by a grant to D. B. West from the Eastern Virginia Diabetes Institutes.

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Received 10 June 1991; accepted in final form 4 December 1991.

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