A Controlled High-Fat Diet Induces an Obese Syndrome in Rats

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ABSTRACT The prevalence of obesity is increasing. Although the etiology of obesity is complex, dietary factors, particularly the consumption of a high-fat (HF) diet, is considered a risk factor for its development. Nonetheless, a causal role of dietary fat has never been definitively documented, in part because of inadequate animal models. We developed a rat model of diet-induced obesity that will be a powerful tool for assessment of this issue. In four experiments, Long-Evans rats ate ad libitum a synthetic semipurified diet containing 20 g (HF) or 4 g [low-fat (LF)] of fat/100 g of diet or a nonpurified diet. Other rats ate ad libitum the HF diet in amounts matched to the energy intake of the LF rats. When compared over 10 wk of free feeding, HF rats weighed 10% more (P < 0.01) than LF rats and had 50% more body fat (P < 0.01), as well as significant hyperleptinemia and insulin resistance. Compared with rats fed the nonpurified diet, the HF rats had even more marked differences in these variables. The rats fed the HF diet to match the rats fed the LF diet had similar body weights but significantly more adipose tissue than LF rats, suggesting that diet composition and/or energy density of the diet affects fat deposition. This dietary regimen has reproducible effects on body size and composition, and these are similar in male and female rats. This model of diet-induced obesity will be a useful tool for studying the mechanisms by which dietary fat influences the regulation of energy balance. J. Nutr. 133: 1081–1087, 2003.

KEY WORDS: • high-fat diet • obesity • insulin • leptin • adiposity • rats

Obesity is a major health problem (1), and despite considerable effort by scientists and health care professionals to understand and successfully treat obesity, its incidence continues to rise and the obesity-related health costs are staggering (2–7). Although it is clear that genetic factors contribute to the propensity of an individual to become obese, the striking increase in overweight that occurs as previously underdeveloped countries modernize and the continued growth in the numbers of obese individuals in developed countries indicate an important role for environmental factors as well. The consumption of a high energy density, high-fat (HF)3 diet is thought to be one of the main factors.

Recent advances in the understanding of energy balance have uncovered many of the regulatory systems involved in body weight homeostasis. A paradox that has emerged from these findings is that although body weight is tightly regulated, when animals, or humans, consume a diet with an HF content on a regular basis, the amount of stored fat they maintain, or defend, increases (8–15). Hence, epidemiological studies have identified a significant positive correlation between mean dietary fat intake and the incidence of obesity and its related complications and risk factors (10,15–22). Furthermore, when the mean amount of fat in the diet increases over time, as has occurred in many countries during the past 30 y, the incidence of obesity also increases (11,23–27). This association of dietary fat with the incidence of obesity is exaggerated in some genetically isolated populations, such as the Pima Indians (28). The key point is that when individuals are exposed, on a chronic basis, to a higher mean level of dietary fat, the otherwise incredibly robust negative feedback system that regulates body fat decreases. More fat is stored and the individual moves along the scale toward obesity. Although diets high in carbohydrates may also predispose an individual to obesity, our focus was on the effects of diets high in fat because of the epidemiological evidence implicating fat in both obesity and public health concerns.

What is not clear is whether or how dietary fat per se is the predisposing factor, in particular because the incidence of obesity has tended to increase in the face of a slightly decreased mean fat intake in the United States (5,29). Dozens of reports have addressed this question in human and animal models over the years, but there has been no consistency of outcomes or conclusions. One reason is that to be persuasive, a model should control precisely both the fat intake and the energy intake of matched groups of subjects, criteria that have rarely been met in experimental studies. Furthermore, in the majority of the published reports considering the effects of HF diets, only one or a few dependent variables were considered, and there has been little continuity either between or over

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3 Abbreviations used: HF, high-fat diet; LF, low-fat diet; PHF, condition in which rats ate ad libitum the low-fat diet; NP, nonpurified diet; PLF, condition in which rats were fed the high-fat diet in amounts restricted to match the mean daily energy consumption of rats in the low-fat group; PLF, condition in which rats were fed the low-fat diet in an amount restricted by an equivalent percentage as the restriction in the PHF group.

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time from the same laboratory group. As a consequence, although it is clear that consumption of an HF diet often leads to obesity, it cannot be unambiguously determined whether it is because of the increased total energy or a greater percentage of energy as fat with total energy held constant. Therefore, we developed a rat model that circumvents many of these shortcomings. More specifically, we describe a model that controls key variables in better reach unambiguous conclusions regarding the role of dietary fat in the etiology of obesity. An important feature of the model is that it is consistent over numerous cohorts, enabling comparisons and generalizations over long time spans. Hence, the model can effectively be applied to determine how consumption of an HF diet modifies the negative feedback system that controls body fat.

In principle, chronic exposure to an HF diet could affect variables at any or all of several levels of control to cause obesity. This could include the taste or other sensory qualities of HF foods, the processing of fat by the gut, the generation and reception of meal-related signals that control food intake and metabolism, the generation and reception by the brain of adiposity-indicating signals and/or brain neurotransmitter systems that regulate food intake and metabolism. Identifying the regulatory processes that mediate HF diet-induced obesity is of fundamental importance and will require a well-established and controlled animal model. The purposes of the experiments described in this report were to establish such a model and to determine whether the rats fed the HF diet share important characteristics with obese humans.

**MATERIALS AND METHODS**

**Rats.** Long-Evans rats (250–350 g) obtained from Harlan Labs (Indianapolis, IN) were housed in individual tub cages with corn cob bedding in a temperature- (22 ± 1°C) and light- (12 h light/12 h dark) controlled vivarium. They ate a nonpurified (NP) diet (Teklad Sterilizable Mouse/Rat Diet; Harlan Labs) and drank water ad libitum for 1 wk before being assigned to dietary groups on the basis of comparable mean body weight in each experiment. All procedures were approved by the University of Cincinnati Internal Animal Care and Use Committee and complied with the Guide for the Care and Use of Laboratory Animals.

**Diets.** Two pelleted semipurified, nutritionally complete experimental diets [AIN-93M (30)] were prepared at Dyets (Bethlehem, PA). The HF diet contained 20 g of fat/100 g of diet (19 g of butter oil and 1 g of soybean oil to provide essential fatty acids) and provided 19.34 kJ/g of diet, including 7.74 kJ/g as fat. The low-fat (LF) diet contained 3 g of butter oil and 1 g of soybean oil/100 g of diet and provided 16.12 kJ/g of diet, including 1.29 kJ/g as fat. Because the emphasis in these experiments was on dietary fat, we equalized the amount of protein and all of the essential minerals and vitamins required for rats (30) per kg for the HF and LF diets (Table 1).

**Experimental groups.** The two groups used for primary comparisons were those that ate the HF or LF diet ad libitum, and they were included in every experiment. Because HF and LF rats were fed different amounts of energy each day, in some experiments a control group received the HF diet, but in amounts limited to the mean daily energy consumption of the rats that ate the LF diet ad libitum. That is, these rats were fed the same proportion of dietary fat as the HF rats but had their energy intake yoked to that of the LF rats. Mean daily energy intake of LF rats was calculated every 3 d, and the yoked rats were given that precise amount of energy each day, but as the HF diet. This was the pair-fed HF group (PHF group). The PHF rats were given their daily food allotment just before lights were turned off, and whereas most of them ate the majority of the food in one large meal early in the regimen, by the end of 10 wk their intake was spread over the day with food occasionally still remaining when new food was offered the next day. Over the course of 70 d, the mean energy intake of the LF and the PHF rats was 83% of the energy intake of the HF rats.

When PHF rats were included in an experiment, an additional control group was also included to control for the fact that the PHF rats, although consuming the same amount of energy each day as LF rats, actually had their food intake limited. That is, given the opportunity, they would eat more of the HF food and would gain weight; hence, they should be considered to be chronically food restricted. Because food restriction per se, independent of dietary conditions, could influence important variables of interest, we included a control group that was fed the LF diet and was energy restricted by the same proportion (~17%) each day as the PHF rats (i.e., the PLF group). In some experiments an additional group of rats ate an NP diet (Teklad Sterilizable Mouse/Rat Diet; Harlan Labs) ad libitum. This diet differed from the semipurified diets in many ways, including nutrient content and energy density. It was included to provide a link to the numerous reports that used nonpurified diets as the only control for an HF diet. Therefore, either three (HF, LF and NP; expt 2–4) or five (HF, LF, PHF, PLF and NP; expt 1) groups were included.

**Experiments**

**Dietary manipulations.** Three cohorts of male (expt 1–3) and one cohort of female rats (expt 4) aged 65–70 d were matched by initial body weight and assigned to dietary groups for 70–80 d. The four experiments were completed over an 18-mo interval. Body weight and energy intake were assessed daily for the first week and then at least twice per week thereafter. At the end of the experiments, rats in expt 1 and 4 were decapitated by guillotine, trunk blood was collected over ice in the middle of the light portion of the day/night cycle and centrifuged and the plasma was stored at −20°C until assayed.

**Response to energy deprivation.** Male rats in expt 3 were assigned by equal initial body weight to HF, LF or NP diets (n = 16/ group) for 70 d. One subgroup of each (n = 8 each) then continued to eat their respective diet ad libitum, and the other subgroup (n = 8 each) ate only 40% of the energy available to their respective controls ad libitum. This regimen was chosen because pilot work indicated that a 60% restriction would cause rapid and reliable weight loss in a short interval. It was continued until the restricted NP rats had lost 12% body weight relative to their free-feeding controls. At that point all three restricted groups were allowed free access to their respective diets.

**Insulin-tolerance tests.** Rats in expt 2 (n = 8 per group) from cohorts of HF, LF and NP groups had food withdrawn for 5–6 h at the beginning of the light period. Tail blood was sampled before and 15, 30, 45 and 60 min after an intraperitoneal injection of regular insulin.
(0.5 pmol/kg in 1 mL saline), and glucose concentration was determined with a handheld glucometer (Accucheck Advantage; Roche Diagnostics Co., Indianapolis, IN). All rats are normally and regained their body weights within 1 d after this regimen.

**Body composition.** Carcasses were individually wrapped and frozen at −20°C. At a later date, each carcass was cut into four approximately equal coronal sections and weighed precisely. These sections were dried to constant weight (4–5 d, typically) using a high-capacity lyophilizer (Labconco, Kansas City, MO). Each dried carcass was then individually wrapped in Whatman paper, placed into a protective cotton sack and placed into a large-capacity Soxlet apparatus, where it was flushed with boiling petroleum ether for 8 h. This duration was sufficient to remove all lipids from the carcass. Each carcass was then thoroughly dried of ether and reweighed. Weight loss after being dried in the lyophilizer was recorded as water weight. Weight loss after being in the Soxlet was recorded as carcass lipid weight. The weight of the carcass after being removed from the Soxlet was the fat-free (lean) tissue weight. For some of the experiments the retroperitoneal and epididymal or ovarian fat pads were dissected and weighed before being returned to the carcass for subsequent analysis of total carcass fat.

**Analyses**

**Plasma hormones.** Plasma insulin was measured by radioimmunoassay using a guinea pig anti-insulin serum with high affinity for rodent insulin (31), and plasma leptin was measured using a rat leptin radioimmunoassay kit from Linco Research, Inc. (St. Charles, MO). Rodent insulin (31), and plasma leptin was measured using a rat leptin radioimmunoassay kit from Linco Research, Inc. (St. Charles, MO).

**Statistical analyses.** Data were analyzed by parametric statistics (ANOVA and repeated measures ANOVA and t-tests, with Tukey's test used as appropriate) as described for each experiment, with α set at P = 0.05, two-tailed.

**RESULTS**

**Energy intake and body weight (expt 1).** HF rats initially were fed more energy per day than LF and NP rats (P < 0.05, wk 1), and this trend persisted for the first 6–7 wk of diet treatment (Fig. 1). LF rats were fed significantly more energy per day than NP rats for the first week and afterwards had comparable energy intakes to NP rats. Body weights of the 3 groups differed after 2 wk, and by the end of 10 wk, the HF rats were significantly heavier than all other groups and the LF rats weighed slightly more than NP rats (P = 0.08) (Fig. 2, Table 2). As expected, PHF rats weighed less than HF rats (P < 0.05) and were not different from the LF rats (P = 0.37). PLF rats weighed less than LF rats (P < 0.05).

**Energy intake and body weight (expt 2–4).** The same pattern of weight gain of HF rats relative to that of LF rats that occurred in expt 1 occurred in expt 2–4, which were conducted at different times of the year (Fig. 3).

**Body composition (expt 1).** Using body weight as the sole indicator of obesity, HF rats weighed 10% more (P < 0.05) than LF rats after 10 wk of being fed the respective diets and ~20% more (P < 0.01) than NP rats. The epididymal pads of the HF rats weighed more than those of all other groups; 45% greater than those of the LF rats and 96% greater than those of the NP rats (both P < 0.01). Similarly, the retroperitoneal pads of the HF rats weighed 29% more than those of the LF rats and 90% more than those of the NP rats (both P < 0.01). The PHF and LF rats were fed the same amount of energy during the experiment (by design), although the proportion of energy as fat was greater for the PHF group. Although the PHF rats tended to weigh less than the LF rats (−4.5%, P = 0.18), they tended to have heavier epididymal (+7.8%, P = 0.16) and retroperitoneal (+4.6%, P = 0.30) pads.

Carcass analyses were conducted on a randomly selected sample of 8 rats per group (Table 2). HF rats had 52% more carcass fat than the LF rats (P < 0.05) and 70% more carcass fat than the NP rats (P < 0.05). When expressed as a percentage of carcass fat, HF rats had 39% more fat than the LF and 44% more fat than the NP rats (both P < 0.05). HF rats had a lower percentage of total weight as water than all other groups (P < 0.01), and carcass fat was inversely correlated with this value across all rats (r = −0.85, P < 0.0001). The PHF rats had 11% more total fat than the LF rats (P = 0.14), although the two groups were fed the same amount of energy during the study. When expressed as a percentage of carcass weight, PHF rats had 16% more fat than LF rats (P = 0.11). When body fat (as a percent of carcass weight) was normalized to that of the NP group (an often-used control group in such experiments (32,33)), the PHF rats had proportionally more fat than the LF rats (23%, P < 0.05).

For comparison purposes, a group of male rats (n = 15) was assessed at the age at which the 70-d dietary treatments began in each experiment. These rats had free access to the NP diet and carcass analysis was completed as described earlier. Mean body weight was 305.7 ± 4.8 g, and mean carcass fat was 1.7 ± 0.4 g/100 g of carcass (or 1.68 ± 0.34% of carcass weight). Hence, rats in all five experimental groups greatly increased both body weight and body fat content over the 70 d (c.f. Table 1).

**Plasma insulin and leptin (expt 1).** HF rats had elevated plasma immunoreactive insulin and immunoreactive leptin...
concentrations relative to all other groups (both P < 0.05) (Fig. 4). Although the other groups did not differ, carcass fat correlated positively with plasma insulin across all rats (r = 0.43, P < 0.01), even though the rats had been food restricted for only 4 h at the time of killing. Plasma leptin was also positively correlated with carcass fat (r = 0.91, P < 0.0001).

**Insulin tolerance test** (expt 2). Blood glucose concentrations after 5-h food restriction were not significantly different among groups (6.0 ± 0.2, 5.5 ± 0.2 and 5.7 ± 0.2 mmol/L in the HF, LF and NP groups, respectively; P = 0.28). In response to insulin, blood glucose did not change in the HF rats (Fig. 5). In contrast, the LF and NP rats had significantly decreased glucose in response to insulin (P < 0.01), with the decrease being significantly greater in the NP than the LF rats (P < 0.05). The area under the curve during the experiment was −0.9 ± 1.7 (mmol/L) · min for the HF group, −4.4 ± 0.8 (mmol/L) · min for the LF group and −9.1 ± 0.6 (mmol/L) · min for the NP group. The area under the curve of each group was significantly different from that of each of the others (P < 0.01), indicating an effect of both the HF and, to a lesser extent, the LF diets in decreasing insulin sensitivity relative to rats that were fed an NP diet.

**Energy intake and body weight in female rats** (expt 4). The energy intake and body weight of females were comparable in every way with those of males with the exception that the absolute weight of the females was less than that of the males. The HF females gained proportionally more weight than the LF females at the same rate as occurred in the HF males relative to the LF males (Fig. 3). The combined weight of the ovarian and retroperitoneal fat pads in HF females was greater than that of the LF and NP groups (by 54% and 122%, respectively; both P < 0.01). Abdominal fat of the LF females weighed more than that of the NP females (P < 0.05). There was more carcass fat in the HF females (61 g) than in the LF (36 g; P < 0.05) or NP females (28 g; P < 0.01). Carcass fat did not differ between the LF and NP females.

**Plasma leptin and insulin in female rats** (expt 4). Plasma leptin concentrations for non food-restricted rats were 24.0 ± 3.4, 10.2 ± 1.5 and 5.2 ± 0.9 μg/L for the HF, LF and NP females, respectively, with the concentration in the HF group greater than those of the other two groups (P < 0.05). Plasma insulin levels for non food-restricted rats were 85 ± 54, 51 ± 6 and 39 ± 7 pmol/L for the HF, LF and NP groups, respectively, with that of the HF rats higher than that of the NP rats (P < 0.05). The levels for the LF rats did not differ significantly from those of the HF or the NP rats. Both plasma leptin (r = 0.75) and plasma insulin (r = 0.48) were directly correlated with carcass fat (both P < 0.05).

**Response to energy deprivation** (expt 3). The body weight responses of rats during short-term food deprivation and return to free access of food did not differ among groups (Fig. 6). The data were normalized to the asymptotic body weight achieved after 70 d of treatment to reveal the relative responses in each group. With an energy restriction to 40% of ad libitum intake, rats in the HF, LF and NP groups lost a mean of 12% of their weight over 2 wk. With return to ad libitum consumption, the HF, LF and NP rats regained lost weight at the same rate. Thus, rats in all three dietary groups defended their body weight equally.

![FIGURE 3](https://academic.oup.com/jn/article-abstract/133/4/1081/4688289)  
**FIGURE 3** Body weights of male rats fed the high-fat diet (HF) in expt 1 (n = 16), expt 2 (n = 8), expt 3 (n = 16) and female rats in expt 4 (n = 8) as a percentage of the body weight of rats fed the low-fat diet (LF) over 10 wk. Values are mean ± SEM. The proportional increase of body weight of HF rats relative to LF rats followed a comparable trajectory for cohorts studied at different times of the year and for males and females.

![FIGURE 4](https://academic.oup.com/jn/article-abstract/133/4/1081/4688289)  
**FIGURE 4** Plasma insulin and leptin in rats in the high-fat (HF), low-fat (LF), pair-fed HF (PHF), pair-fed LF (PLF) and nonpurified (NP) groups in expt 1. Values are means ± SEM, n = 8. Insulin and leptin values with a different letter differ significantly, P < 0.05.

<table>
<thead>
<tr>
<th>Item</th>
<th>HF diet</th>
<th>LF diet</th>
<th>NP diet</th>
<th>PHF diet</th>
<th>PLF diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>638 ± 23a</td>
<td>582 ± 11b</td>
<td>529 ± 15bc</td>
<td>556 ± 12b</td>
<td>515 ± 7c</td>
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<td>Carcass fat, g</td>
<td>92.4 ± 9.0a</td>
<td>60.8 ± 7.2b</td>
<td>54.3 ± 6.6bc</td>
<td>67.5 ± 4.8b</td>
<td>41.4 ± 1.3c</td>
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<tr>
<td>Fat, g/100 g of carcass</td>
<td>15.3 ± 1.2a</td>
<td>11.0 ± 1.2b</td>
<td>10.6 ± 1.0b</td>
<td>12.8 ± 1.0b</td>
<td>8.6 ± 0.2c</td>
</tr>
<tr>
<td>Water, g/100 g of carcass</td>
<td>50.8 ± 1.2c</td>
<td>54.9 ± 1.0b</td>
<td>57.5 ± 1.3ab</td>
<td>53.5 ± 0.8b</td>
<td>58.1 ± 0.9a</td>
</tr>
<tr>
<td>Fat normalized to the NP group, %</td>
<td>146.2 ± 10.9a</td>
<td>97.6 ± 7.6c</td>
<td>100 ± 8.7bc</td>
<td>119.7 ± 9.0b</td>
<td>81.8 ± 2.3d</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 8. Means in a row without a common superscript letter differ, P < 0.05.
DISCUSSION

We describe here a model of diet-induced obesity in rats that is reproducible over several experiments, is well controlled and shares many features with human obesity. HF rats weighed more than LF controls and defended this weight in the face of changes in energy availability. In addition, they developed substantially more adipose tissue than control rats and acquired the insulin resistance and hyperleptinemia typically associated with obesity. By comparing these rats with those in the LF and PHF groups, we were able to distinguish between the effects of obesity and dietary composition on these, and potentially other variables. This model is therefore well suited for a systematic investigation of the role of dietary fat on body weight regulation and can be applied to many questions that are central to obesity research.

Rats with free access to an HF diet were fed more energy and became obese relative to rats with free access to a diet containing the same constituents but less fat. The obesity was manifest as a modest but nonetheless significant 10% increase in total body weight. However, body weight per se can be misleading and in this case greatly underestimated the actual degree of obesity that developed in HF rats. Specifically, the fat pads of HF rats weighed 30–45% more than those of LF rats, and their total carcass fat was >50% greater than that of the LF rats. These differences were even more marked relative to rats fed the NP diet, the control traditionally used in studies of rodent diet–induced obesity. Thus, rats consuming the HF diet gained increased body fat relative to rats eating either of two quite different LF diets.

The most parsimonious explanation for the ability of the HF diet to induce obesity is overconsumption of this diet rather than specific metabolic effects of differing proportions of fat and carbohydrate in the diet. This interpretation is based on the similar body weights and composition of LF rats compared with rats that ate the HF diet in amounts that were matched to the intakes of the LF group. However, these PHF rats had more carcass fat than LF rats, albeit the difference was significant only when both were compared with NP controls. Nonetheless, we contend that this difference is genuine and will be confirmed when further cohorts of rats are studied because rats in every cohort had group weights comparable to those whose carcasses were analyzed. Furthermore, the conclusion would be consistent with previous studies demonstrating that fat accumulation is greater when more energy comes from dietary fat than from carbohydrate or protein (34,35).

We cannot exclude the possibility that the “meal-feeding” pattern that the PHF group naturally adopted contributes to increased body adiposity. We consider this unlikely, however, because even though the ration of food was presented at the same time each day, over the course of 10 wk, the PHF rats modified their pattern of intake so as to spread energy consumption over the entire day. Furthermore, the PLF rats had a similar percentage of body fat relative to the LF rats (78 ± 3%) as the PHF rats did to the HF rats (84 ± 4%), suggesting that food restriction and a meal-feeding pattern did not contribute measurably to body fat content. A more comprehensive analysis in future experiments is needed to reveal if dietary fat content contributes more to body fat than energy content per se. Questions such as this bear further consideration and are readily addressed using our model.

A second possible explanation as to why the HF rats became obese relates to the energy density of the diet. It has been suggested that energy density, rather than simply an increased percentage of dietary fat, is the actual predisposing factor for weight gain in several animal studies (36–40). Although it is possible to independently vary energy density and the relative percentage of dietary fat, in our model the HF diet had an increase in both variables because we did not adjust the nonfat constituents of the diet to compensate for the increased energetic value of the additional fat. This distinction between energy density and fat percentage is important because in previous studies, when energy density was controlled, it appeared that food intake by animals was regulated primarily by volume (36,40), a phenomenon that holds for humans as well (41–44). The present data are consistent with this interpretation because the increased energy intake by the HF rats is consistent with the increased energy density of the HF diet.

The greater difference between the HF and NP rats compared with the HF and LF groups emphasizes the importance...
of careful matching of dietary constituents. The difference in body weight and carcass fat between the LF and NP rats can logically be ascribed to the relatively greater palatability of the LF diet and/or to the specific sources of macronutrients in the two diets. The differences in plasma leptin concentrations and insulin sensitivity are consistent with increased body adiposity in the LF relative to NP rats. Previous studies using only an NP group as a control may have overestimated the effects of their experimental diets because of major differences in palatability or nutrient availability. The current results permit a more precise assessment of the effect of dietary fat content on body weight and adiposity.

The model described by these experiments shares many important features with human obesity. Perhaps most important, the phenomenon is reliable and consistent from one experiment to the next. This validates making comparisons across experiments when the same diets and procedures are used to produce the obese state. The paradigm also appears to be equally effective at least on a relative level, in males and females. This is important because both men and women, when they eat diets high in fat, have a tendency to become obese. The obese rats are both hyperleptinemic and hyperinsulinemic, and, as occurs in humans, both plasma insulin and leptin concentrations were directly correlated with the degree of adiposity. In all likelihood, the hyperinsulinemia in the HF rats was a result of insulin resistance, a common feature of human obesity that one is central to the development of diabetes and cardiovascular disease. The PHF group was not hyperinsulinemic and presumably had a similar degree of insulin sensitivity as the LF group. It will be important to test this question formally because the possibility that insulin resistance can be induced by HF diets, independent of obesity, is controversial in nutritional research (45,46).

An important and unfortunate feature of human adiposity is that when an individual has lost weight through dieting (voluntary food restriction), body weight tends to return to baseline levels over time. This is true of both lean and obese humans. A similar outcome was also observed in two separate experimental groups of rats in which mice were restricted and lost weight. Obese and lean rats alike returned to basal weights in a similar manner. Although this finding only confirms a feature that is common to many models of experimental obesity, it is a critical variable to establish if our model is to provide useful extensions to human obesity. Using our paradigm, it will be possible to determine the mutability of defended body weight and other related questions that are of critical importance in designing rational weight reduction strategies.

In summary, we developed a model of HF diet-induced obesity having several features that make it useful for investigating the mechanisms by which dietary composition contributes to body weight regulation. Of central importance is a comparison of control rats that consume diets differing in percentage of fat and the inclusion of rats with fixed intake of the HF diet to prevent obesity. This model will allow a detailed investigation of specific regulatory body weight systems to discern the site or sites at which dietary fat alters homeostasis.

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Literature Cited


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