Initiation and perpetuation of obesity and obesity resistance in rats

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LEVIN, BARRY E., SUE HOGAN, AND ANN C. SULLIVAN. *Initiation and perpetuation of obesity and obesity resistance in rats.* Am. J. Physiol. 256 (Regulatory Integrative Comp. Physiol. 25): R766–R771, 1989.—A search was made for predisposing factors and sequelae of diet-induced obesity (DIO) or resistance to DIO (DR). During 3 mo on a high-energy (CM) diet, two-thirds of the male Sprague-Dawley rats ate 16% more calories over the first 30 days and developed DIO. The remaining one-third were DR, gaining the same amount of weight as chow-fed controls. Basal and norepinephrine (NE)-stimulated in vivo O_2 consumption, performed before rats were placed on the CM diet, was the same in those rats that later became DR or DIO after 3 mo on the CM diet. DR rats were 4% lighter, whereas DIO rats were equal to chow-fed rats before their exposure to the CM diet. When CM-fed rats were switched to chow, DIO rats took 14 wk to reduce their body and retroperitoneal fat pad weights to those of chow-fed controls, whereas DR rats gained only 40% of the body weight, and fat pads were 34% lighter than controls. After 14 wk, DIO rats were neither hyperinsulinemic nor insulin resistant, whereas DR rats had 64% reduced areas under their insulin curves after intravenous glucose (1 g/kg) compared with controls. Unlike younger rats, animals here had inconsistent plasma NE responses to intravenous glucose. Therefore the CM diet produces DR and DIO states that tend to become self-perpetuating once established.

sympathetic nervous system; norepinephrine; insulin; glucose; oxygen consumption; thermogenesis

ONE OF THE MAJOR ISSUES in the field of obesity is why some humans become obese and others resist the development of obesity when exposed to high-calorie diets (26). In rats, a similar disparity is seen among otherwise homogeneous groups of male Sprague-Dawley rats fed a high-energy diet. About half of the rats fed a diet relatively high in calories, fat, and sucrose content [condensed milk (CM) diet] (20), develop diet-induced obesity (DIO), whereas the remainder resist the development of obesity [diet resistant (DR)] (13–15, 17, 20, 21). DR rats usually eat the same or somewhat fewer numbers of calories and gain the same amount of weight as chow-fed controls (13, 21). DIO rats eat the same, fewer, or, at times, more calories than controls (13, 21). Regardless of their intake, they still become obese. This obesity is associated with hyperinsulinemia, insulin resistance, and reduced pancreatic sympathetic activity (13, 17, 20, 21, 29). Once the DR and DIO conditions are established, DR rats tend to gain weight more slowly than chow-fed controls and DIO rats tend to remain obese when they are switched back to chow for up to 7 wk (17).

We recently found that intravenous administration of glucose to chow-fed rats led to activation of the sympathetic nervous system with release of norepinephrine (NE) into the plasma (16). The degree of activation correlated with subsequent development of DIO (14). Rats with the highest glucose-induced NE levels had the greatest and, those with the lowest NE levels, the least weight gain when fed the CM diet for 3 mo (14). This relationship between glucose-induced NE levels and weight gain was also maintained when rats were tested subsequent to the manifestation of the DIO or DR states (15).

Because the sympathetic nervous system is a major effector of thermogenesis (3) and because DIO rats (5), like genetically obese Zucker rats (4), have diminished metabolic rates, it seemed counterintuitive that DIO rats would have higher rather than lower NE levels when given glucose. One hypothesis would be that DR and DIO rats have different levels of sympathetic activation because of differential sensitivity to NE at thermogenically active sites. The current studies were designed to test this hypothesis by evaluating the in vivo thermic sensitivity to NE of chow-fed rats, before their exposure to the CM diet, and correlating it with subsequent weight gain on the CM diet. We also wished to see how long it would take DIO rats to become nonobese and whether DR rats would finally revert to a weight gain pattern similar to chow-fed controls after they were switched to chow from the CM diet. Toward this end, chow-fed rats were tested for thermic capacity, fed the CM diet for 3 mo to become DIO or DR, and were then switched to chow for an additional 14 wk.

METHODS

Animals, diet, and experimental procedure. A total of 36 male Sprague-Dawley rats began the study at 400–450 g. These animals were of the same age and delivered from the supplier (Charles River Labs) in the same batch. Animals were individually housed at 22–23°C on a 12:12 h light-dark cycle and fed Purina rat chow for the first phase of the study during which in vivo O_2 consumption was measured. For the second phase, 28 rats were switched to a semisynthetic diet composed of 47% rat

chow, 8% corn oil, and 44% sweetened condensed milk (CM diet) (20, 28) for a period of 3 mo. This diet contains 4.47 kcal/g (gross energy content) and 20.6% protein, 31.1% fat, and 48.3% carbohydrate by apparent gross energy content. Food intake was monitored for the first 30 days after the switch to the CM diet ($n = 28$) and in those rats left on chow ($n = 8$). After 3 mo, body weight gain histograms were plotted for chow-fed vs. CM diet-fed rats, and CM-fed rats were assigned to DR and DIO groups according to whether their weight gain was the same as or greater than chow-fed controls, respectively (see *Statistics*). This method of dividing rats into DIO and DR groups has been shown to accurately reflect the degree of obesity of rats fed the CM diet on the basis of carcass lipid content (13). All rats were then placed on chow for an additional 14 wk.

In vivo O_2 consumption. Indirect calorimetry was performed to estimate thermogenic capacity. For estimation of O_2 consumption, anesthetized (pentobarbital sodium, 61 mg/kg ip) rats were placed in individual chambers, and O_2 consumption was monitored for 3.5 h. Room air at 24°C was drawn at a flow rate of ~1,000 ml/min sequentially through each of seven Plexiglas animal chambers. One of the chambers remained empty for continuous reference to O_2 and CO_2 concentrations in room air. The cycle time required for air to be sampled from all chambers was set at 4 min. The O_2 analyzer (model S-3A, Applied Electrochemistry) was calibrated with gas mixtures before each series of measurements using class "A" primary standards (Liquid Carbonic). The rate of airflow, relative humidity, barometric pressure, and temperature of the air leaving the chambers were measured by a mass flowmeter (model ST-5K, Teledyne-Hastings), humidity sensor (model PC-2101, Thunder Scientific), pressure transducer (model 1800, Foxboro), and a thermistor (model P100 BA 103J, Thermometrics) positioned directly before the analyzers. A relative humidity of ~28% was maintained throughout the measurements by circulating cold water through condensors positioned behind the chambers. CO_2 production (model CD-3A, Applied Electrochemistry) was also monitored so that the Haldane correction could be used to account for the difference in airflow between the inlet and the outlet when the respiratory quotient was <1.0. O_2 consumption at STPD was expressed per animal (ml/min) and in terms of metabolic mass ($ml \cdot min^{-1} \cdot kg^{-0.75}$). In preliminary experiments, a separate group of rats was then given NE bitartrate at doses of 150, 300, or 450 μg/kg subcutaneously, and O_2 consumption was monitored for an additional 2.0 h. Based on these initial results, a final dose of NE of 200 μg/kg was chosen for the experimental group. Experimental animals ($n = 28$) were then anesthetized and monitored for basal and NE-stimulated O_2 consumption as above.

Intravenous glucose tolerance test. After 3 mo on the CM diet or chow and an additional 14 wk on chow, all animals underwent an intravenous glucose tolerance test (14, 16). First, under Chloropent anesthesia (0.3 ml/100 g body wt ip), rats had PE-50 catheters placed in their right atria via the right jugular vein. Catheters were filled with heparinized saline (500 U/ml), plugged, secured to underlying muscle, and tunneled subcutaneously to the nape of the neck. Animals were allowed to recover for at least 2 days, by which time body weight gain and food intake were back to presurgical levels. Food was removed at 0600 h on the day of testing, and 4 h later a basal blood sample (0.5 ml) was withdrawn into ice-cold heparinized tubes. Rats were then given glucose (1 g/kg of 50% glucose in 1.2–1.7 ml of 0.9% saline) intravenously and more 0.5 ml samples were drawn at 2, 5, 10, 30, and 60 min after glucose infusion (14, 16). This dose of glucose was chosen because it gives reproducible activation of the sympathetic nervous system (14, 16) that is independent of the stress of the procedure (16). Plasma was removed and frozen at −70°C for insulin and glucose determinations or combined with 5 N perchloric acid to a final concentration of 0.1 N and stored at −70°C for NE determinations. Plasma volume was maintained during the testing by replacement with 0.9% saline and homologous washed red cells were returned to the rats after the 10- and 30-min samples to maintain red cell mass (18). At the conclusion of the study rats were decapitated, and the retroperitoneal pads removed and weighed.

Assay of plasma constituents. Plasma catecholamines were assayed in 50 μl of the perchloric acid supernatant of plasma by radioenzymatic assay (18). Plasma insulin levels were determined in 100 μl of plasma by double-antibody radioimmunoassay using authentic rat insulin (Novo) as the standard (12). Plasma glucose levels were determined by automated glucose oxidase method (Beckman).

Statistics. Values for plasma constituents were converted to "area under the curve" as a function of change from base-line levels over 60 min of testing by the trapezoidal method (8). Data for an individual animal were excluded if data from one or more time points were missing. Glucose fractional disappearance rates (k) were calculated as the negative slope of the regression of the natural log of plasma glucose values vs. time, beginning at peak levels (2 min postglucose) and ending with the return to base line. Assignment of rats into DR and DIO categories was carried out by construction of body weight gain histograms after 3 mo on the CM diet vs. chow-fed controls. This gave a bimodal histogram for the former and unimodal histogram for the latter as has been described previously (13, 14). This was confirmed by Pearson's χ^2 analysis for CM-fed rats (72.46, df = 25, $P = 0.0001$). DR rats were defined as those animals with weight gains equal to or less than the heaviest chow-fed controls and DIO rats as those with greater weight gains (13, 14, 21). Estimates of areas under the curve, k values, body and fat pad weights were compared among the three groups (chow, DR, DIO) by one-way analysis of variance (ANOVA) and curves for constituents during the glucose tolerance test by ANOVA for repeated measures. When significant intergroup differences were found by ANOVA ($P \leq 0.05$), the data were further analyzed by post hoc t test. Correlations were performed by Pearson's correlation.

RESULTS

Of the 28 rats fed the CM diet, 68% became obese (DIO) after 3 mo on the CM diet. The remaining rats

resisted the development of obesity (DR), gaining the same amount of weight as chow-fed animals (Table 1, Fig. 1). Those rats that eventually became DR were 4% lighter in weight than chow-fed and 7% lighter than prospective DIO rats before being placed on the CM diet [$F(2,33) = 5.079$, $P = 0.012$]. DIO-prone rats were equal in weight to controls before their exposure to the CM diet on which they ate 16% more calories than either chow-fed or DR-prone rats during their first 30 days on the diet [$F(2,33) = 4.380$, $P = 0.020$]. After 3 mo on the CM diet, DIO rats had gained 90–95% more weight than chow-fed and DR rats [$F(2,33) = 32.605$, $P = 0.0001$]. When O_2 consumption data were analyzed retrospectively according to weight gain on the CM diet, there were no differences between responses in DR and DIO rats. Neither basal values nor values for maximal NE stimulation nor areas under the curve after NE injection [DR = 337 ± 37 (n = 9); DIO = 331 ± 26 ml·min^{-1}·kg$^{-0.75}$/2 h (n = 19)] differed significantly. Both groups increased their metabolic rate by 27–30% after NE infusions (Fig. 2). Therefore thermogenic capacity did not differentiate these animals when they were still fed chow.

Despite their strikingly different patterns of weight gain during 3 mo on the CM diet, once DR and DIO rats were switched back to chow, they showed very similar weight gain patterns for the ensuing 14 wk; DR rats gained only 40% and DIO rats, only 25% of the weight of chow-fed rats during this same period (Fig. 1, Table 1; $F(2,33) = 4.987$, $P = 0.013$). Total weight gain over the entire 26-wk period (12 wk on CM and 14 wk back on chow) for the DIO rats was still 24% greater than chow-fed and 62% greater than DR rats [$F(2,33) = 4.331$, $P = 0.021$]. Final body weight and retroperitoneal fat pad weights of the DIO rats was the same as chow-fed rats (Table 1). The DR rats, on the other hand, gained so little weight after their return to chow that their final body weight was only 88% [$F(2,33) = 4.239$, $P = 0.023$] and their fat pads weights only 66% of chow-fed rats [$F(2,33) = 5.623$, $P = 0.008$].

After the entire 26-wk experimental period, rats underwent an intravenous glucose tolerance test with 1 g/kg of glucose (Fig. 3). Glucose infusion produced virtually identical plasma glucose responses in the three groups with similar areas under the curve and fractional disappearance rates (k; Table 2). There was a nonsignificant tendency for k values to be increased in DR rats. Plasma insulin curves over the 60-min test period (Fig. 3) were significantly different among the three groups [$F(2,27) = 4.325$, $P = 0.023$] due to generally lower levels in both DR and DIO compared with chow-fed rats, and, specifically, the area under the curve for DR insulin levels was only 44% that of chow-fed rats ($P = 0.01$). Body weight gain over the entire 26-wk period showed a significant [$F(1,28) = 4.962$, $P = 0.036$], positive correlation (r = 0.675) with the areas under the insulin curves among the three diet groups, whereas no such relationship for glucose areas or k values was found. As opposed to the fairly homogeneous responses of glucose and insulin to glucose

TABLE 1. *Food intake and body and retroperitoneal fat pad weights in chow-fed rats and rats fed the CM diet for 3 mo followed by 14 wk on chow*

	Chow	DR	DIO
n	8	9	19
Initial body weight, g	497±7	466±8*	486±4†
Body weight gain on CM × 3 mo, g	142±10	146±9	277±14*†
Body weight gain on chow × 14 wk, g	102±9	41±7*	26±14*†
Body weight gain total (26 wk), g	244±16	187±11*	303±13*†
Final body weight, g	740±22	653±14*	789±16†
Food intake, first 30 days on CM, kcal·rat^{-1}·day^{-1}	109±3	110±4	127±4*†
Retroperitoneal fat pad weight, g	17.2±2.0	11.3±1.4*	22.4±2.4†

Values are means ± SE; n, no. of rats. Chow, chow-fed rats; DR, diet resistant; DIO, diet-induced obesity. * $P < 0.05$ when DR or DIO values were compared with chow-fed values and † $P < 0.05$ when DR values were compared with DIO values by post hoc t test after significant intergroup differences were found by 1-way ANOVA.

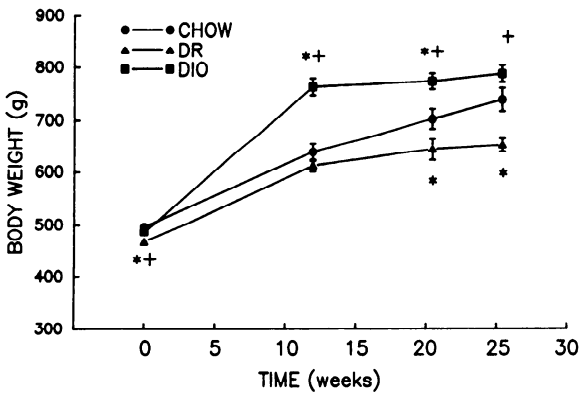

FIG. 1. Body weights of rats fed chow (n = 8; ●) or condensed milk (CM) diet for 3 mo (12 wk) and then switched to chow for an additional 14 wk. After 3 mo on chow, CM-fed rats fell into a diet-resistant (DR; n = 9; ▲) group, which gained same amount of weight as chow-fed rats and a diet-induced obesity (DIO; n = 19; ■) group, which gained considerably more weight. Data points are means ± SE (vertical bars). * $P < 0.05$ or less when DR or DIO rats were compared with chow-fed controls; † $P < 0.05$ or less when DR rats were compared with DIO rats.

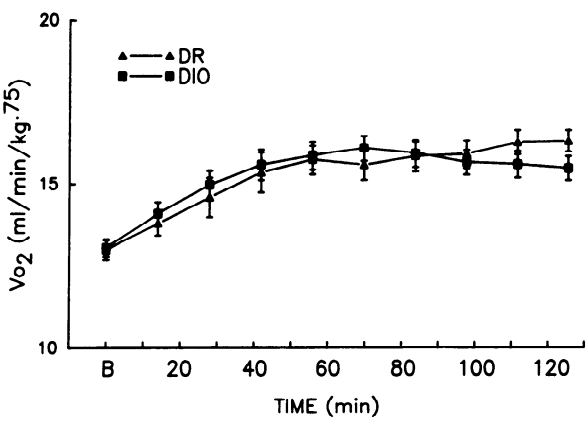

FIG. 2. O_2 consumption ($\dot{V}O_2$) in rats tested while on a chow diet and then retrospectively put into diet resistant (DR; n = 9; ▲) or diet-induced obesity (DIO; n = 19; ●) groups by their weight gain patterns after 3 mo on condensed milk diet compared with chow-fed controls. B, average basal $\dot{V}O_2$ (ml·min^{-1}·kg$^{-0.75}$) taken over a 3-h period in pentobarbital-anesthetized rats. Rats were then given norepinephrine (200 μg/kg sc), and their $\dot{V}O_2$ was monitored for an additional 2 h. Data points are means ± SE (vertical bars).

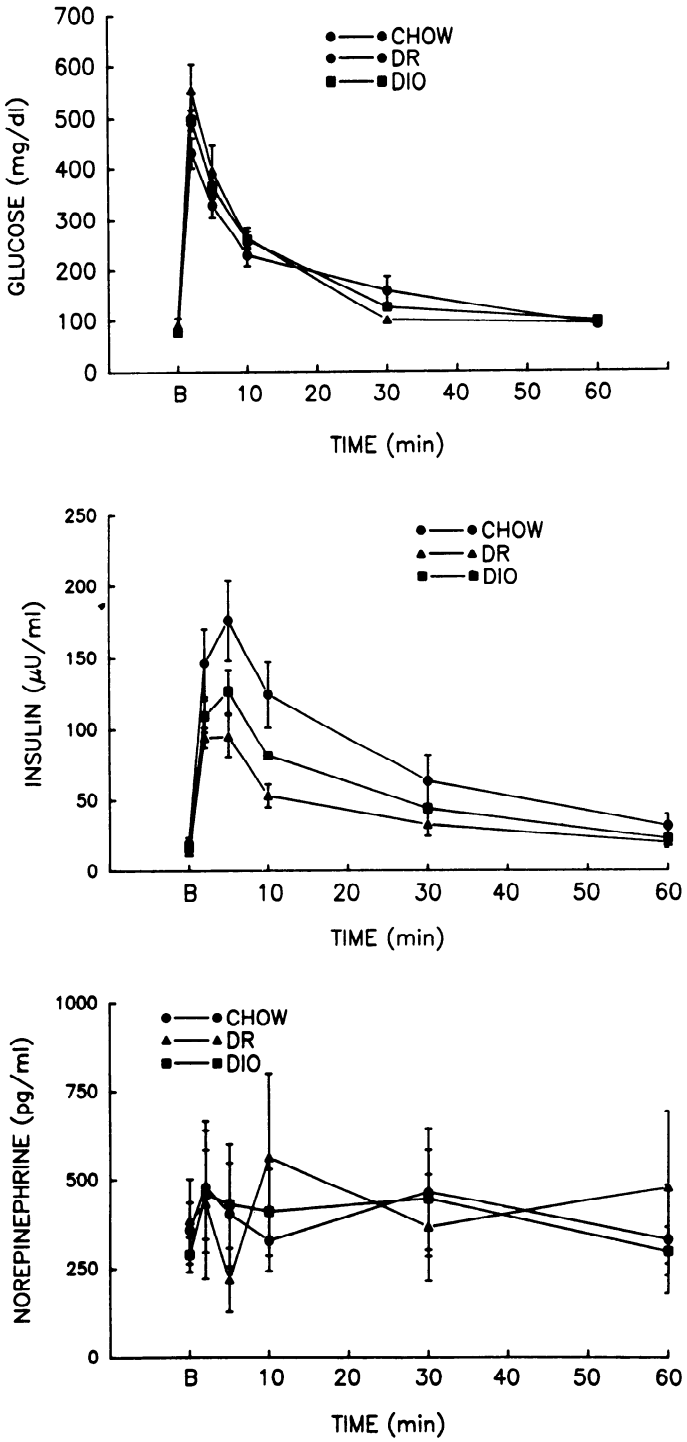

FIG. 3. Plasma glucose, insulin, and norephinephrine levels at base line (B) and for 60 min after 1 g/kg of intravenous glucose in rats that had been fed chow for 26 wk (n = 7; ●) or condensed milk (CM) diet for 12 wk followed by chow for 14 wk and had developed diet resistance (DR; n = 7; ▲) or diet-induced obesity (DIO; n = 15; ■) after CM diet feeding. Data points are means ± SE (vertical bars).

infusion, NE levels showed enormous individual variability after glucose (Fig. 3). Although there was a tendency for increased areas under the curve in DR and DIO rats, the huge variability resulted in no significant increase in levels from base line over the 60-min test period. Neither did any of the NE curves differ from each other or from those in chow-fed rats over this period. Nor was there any relationship between NE areas and weight gain.

TABLE 2. *Plasma glucose fractional disappearance and glucose, insulin, and NE areas under curve after intravenous glucose*

	Chow	DR	DIO
n	7	7	16
Glucose k, %/min	0.042±0.003	0.053±0.005	0.046±0.002
Glucose area, mg·dl^{-1}·60 min^{-1}	5,481±526	4,510±674	5,829±532
Insulin area, μU·ml^{-1}·60 min^{-1}	3,477±617	1,529±259*	2,152±372
NE area, pg·ml^{-1}·60 min^{-1}	1,535±6,825	4,456±7,030	6,683±6,539

Values are means ± SE; n, no. of rats. Chow, chow-fed rats; DR, diet resistant; DIO, diet-induced obesity. * $P < 0.05$ when DR values were compared with chow-fed values by post hoc t test after intergroup differences were found by 1-way ANOVA.

DISCUSSION

Feeding male Sprague-Dawley rats a high-energy CM diet for 3 mo produced two different patterns of weight gain in an otherwise homogeneous population of animals. Two-thirds became obese, whereas the remainder resisted the development of DIO. Once the phenotypic expression of the DR and DIO traits was manifested, DIO rats almost ceased gaining weight but still remained obese for almost 14 wk after being switched from the CM diet to chow. Paradoxically, DR rats decreased their weight gain when switched back to chow. The result was that it took the DIO rats 14 wk to bring their body and fat pad weights near those of chow-fed controls, and, over the same time span, DR rats gained only 40% of the body weight and had retroperitoneal fat pads that were 34% lighter than chow-fed rats. This occurred despite the fact that DR rats were the same body weight as chow-fed rats after 3 mo on the CM diet.

In vivo thermogenesis of prospective DR and DIO rats was identical before their exposure to the high-energy CM diet and there was no correlation between thermic capacity of chow-fed rats and their subsequent weight gain on the CM diet. Because the sympathetic nervous system is a major effector of thermogenesis (3, 6) and prospective DR rats have been shown to have lower glucose-induced plasma NE levels (14, 15), we proposed that differential in vivo thermic sensitivity to NE might have predisposed DR and DIO rats to gain weight differently. But the current studies show that this is not the case. However, Hogan et al. (5) have shown that, after 5 mo on the CM diet, basal metabolic rates in DIO rats are decreased, whereas NE-stimulated thermogenesis is increased by ~15% in both DR and DIO rats compared with chow-fed rats. Thus altered thermic capacity appears to be a result, rather than a cause, of the expression of these two patterns of weight gain.

We previously showed (14) DR-prone rats have lower levels of glucose-induced NE levels. But this finding does not appear to affect the thermic capacity of such rats as we had predicted. In fact, by the time the rats in the current study were assessed, plasma NE levels failed to show any consistent pattern in response to glucose in

any of the rats, regardless of their prior dietary history. Plasma NE levels represent NE released primarily from sympathetic nerve terminals throughout the body (10) minus clearance by the kidney and reuptake in tissues and sympathetic nerve terminals (7, 9). Vascular sympathetic nerves are a major source of plasma NE (9) and depressed activity in these nerves is the only abnormality in sympathetic function seen in DR rats under steady-state conditions (21). Thus reduced glucose-induced NE levels in prospective DR rats (14) could be due to diminished NE release from vascular sympathetic nerves. On the other hand, it is surprising that prospective DIO rats have been shown to have higher glucose-induced NE levels than DR rats (14), since fully developed DIO is associated with diminished pancreatic, cardiac, and vascular sympathetic activity (17, 20, 21). Another possibility is that prospective DR and DIO rats have different clearance rates of NE from the plasma similar to that seen in Zucker rats (22), whereas the obese rats have reduced NE clearance as well as reduced sympathetic activity in several organs (19, 22). Finally, the lack of a consistent glucose-induced NE response in any of the rats in this study may be a function of age, since they were 10 mo old here, whereas younger rats (3–6 mo) show more consistent patterns of sympathetic activation to glucose (14–16). Certainly, it seems unlikely that altered plasma NE responses to glucose explain the differences in weight gain patterns of DIO and DR rats switched from the CM diet to chow in the current study.

Disparate weight gain patterns in diet-switched DR and DIO rats might be explained by differences in caloric intake. But even though DIO rats had higher intakes than chow-fed and DR rats during the first 30 days on the CM diet in this study, this has not been a consistent finding on the CM diet. DIO rats can become obese without hyperphagia (13), whereas DR rats have been either hypophagic (13) or euphagic (21) in some studies. The real question is why DIO and DR rats regulate their food and intake and energy metabolism as they do. Generally, decreased caloric intake would be associated with increased metabolic efficiency (decreased thermogenesis) (2, 29) and decreased sympathetic activity (11). In a similar study to the present one (17), DIO rats switched from the CM diet to chow decreased their caloric intake transiently (2 wk) by only 4% and did not change their food efficiency and so remained obese over a 7-wk period. DR in that study decreased their caloric intake over the entire 7-wk period to 13% of chow-fed controls, increased sympathetic activity in brown adipose and heart, and decreased their food efficiency by 49% (17). The result was a diminished rate of weight gain in DR rats over the ensuing 7 wk, similar to that seen in the present study. Thus the combination of decreased energy intake and increased expenditure could account for the low level of weight gain of DR rats after their switch to chow from the CM diet seen here. It remains unclear, however, why DR rats appear to defend a lower body weight, whereas DIO rats appear to defend a higher one after switching diets.

The development of insulin resistance could be a contributing factor to the defense of raised body weight in DIO rats after their switch to chow from the CM diet. Glucose utilization is an important source of diet-induced thermogenesis, which is, in turn, strongly influenced by insulin sensitivity in various tissues (25). DIO rats are hyperinsulinemic and/or insulin resistant after 3 mo on the CM diet (15, 17, 28) and were previously shown to maintain this hyperinsulinemia for 7 wk after being switched back to chow, at a time when they were still obese (17). But prospective DIO rats are not insulin resistant (14) and, after 14 wk of chow feeding in the present study, DIO rats were no longer obese nor hyperinsulinemic and their insulin sensitivity appeared to be normal. Interestingly, even DR rats develop increased carcass lipid but not elevated body weights if kept on the CM diet for 5 mo (13). Even though they do not exhibit basal hyperinsulinemia after 3 mo (15, 17, 28) or 5 mo (13) on the CM diet, DR rats do develop mild insulin resistance (15), probably due to the relatively high fat content of the CM diet (27). Nevertheless, they still have decreased rather than increased food efficiency in the face of decreased food intake when switched from the CM diet to chow (17). Therefore insulin resistance does not appear to cause obesity in DIO rats or explain why DR rats do not become obese. However, once it develops, insulin resistance probably contributes to the decreased metabolic rate (5) and slowed weight loss in DIO rats switched to chow from the CM diet.

Although it is clear that DR and DIO rats differ markedly in their regulation of food intake and metabolic efficiency once exposed to a high energy diet, it is less clear what the underlying mechanism of these differences might be. We have found that phenotypic expression of the DR and DIO traits is dependent on strain, age, and diet. The bimodal weight gain pattern that male Sprague-Dawley rats exhibit on the CM diet is not seen before ~6–12 wk of age (21, 24), does not occur in some other strains of rats (21), and is not expressed when rats are kept solely on chow for up to 8–10 mo of age (13). Although DIO rats in the present study were heavier than DR rats before exposure to the CM diet, this is not a consistent finding (13). Clearly, this weight gain trait is preexisting because it can be identified before exposure to the CM diet by differences in the centrally mediated release of NE to a glucose load (14, 15). Furthermore, prospective DIO rats have a greater "cephalic" insulin response to oral saccharin than prospective DR rats (1).

These findings suggest that the central nervous system may be an important site for mediation of the changes in food intake and metabolic efficiency that produce the DR and DIO states. Preliminary evidence from our laboratory suggests that prospectively identified, chow-fed DR and DIO rats differ in the degree to which a conditioned food stimulus activates various autonomic centers in the brain. After 3 mo on the CM diet, DIO and DR rats differ in both catecholamine metabolism (18) and adrenoreceptor binding (30) in several hypothalamic areas implicated in the control of food intake and body weight regulation. Thus DR and DIO rats may have preexisting differences in central processes related to body weight regulation that are accentuated and perpetuated by chronic exposure to a high-energy diet. Al-

though it is unclear what the relative contribution of peripheral metabolism is to this change in weight gain patterns, we propose that the events surrounding exposure to a high-energy diet produce alterations in central pathways controlling body weight regulation and thus represent an example of environmentally induced plasticity of the central nervous system in adult rats.

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