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Reduced Organ Growth When Hyperphagia Is Prevented in Genetically Obese (fa/fa) Zucker Rats[1] (41224)

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Abstract. Restricting the food intake of the genetically obese rat throughout life to that eaten by its lean littermate normalized body weight but not body composition compared to lean controls at 15 weeks of age. However, by 33 weeks of age the body weights of the restricted fatties were greater than those of lean controls but less than those of *ad libitum*-fed fatties. The weights of muscle, kidney, liver, and brain were decreased in restricted fatties. For the muscle and kidney significant decreases in DNA and protein content occurred in restricted fatties in comparison with both *ad libitum*-fed lean or obese controls. In the brain and liver more subtle but significant growth alterations were noted. Consequently, the ability of the calorically restricted obese rat to maintain its obese body composition occurs at the expense of normal growth in other organs and tissues.

Most studies on the treatment of obesity have focused primarily on the effects of decreased caloric intake on body weight, body fat, and adipose tissue cellularity. Furthermore, the intractability of early-onset hyperplastic-hypertrophic obesity has brought increased attention to the need for prevention of this type of obesity early in life, primarily through regulation of food intake. However, in the developing individual, dietary intervention could possibly compromise growth of other organs and tissues in addition to adipose tissue as indicated by previous studies where early nutritional insults significantly affected overall growth and growth of specific organs and tissues (1–5).

The genetically obese Zucker rat has frequently been used as a model of early-onset hyperplastic-hypertrophic obesity. Previous studies of either pre- or postweaning (6–9) food restriction in the obese Zucker rat did not result in prevention of obesity. In this study the effects of combining both pre- and postweaning dietary intervention were studied in the obese Zucker rat. The consequences of this treatment for the development of the obesity and specific effects on muscle, kidneys, brain, and liver growth were investigated.

Materials and Methods. Rats used in these studies were the progeny of matings between obese (fafa) males and heterozygous lean (Fa/fa) females of the Zucker genetically obese strain obtained by use of the hormone supplementation method described by Hemmes *et al.* (10). At birth rats were placed into litters of 8 per dam (control litters) and 18 per dam (restricted intake litters) as previously described (11). At 28 days, pups were weaned.[4] Pups from control litters were allowed *ad libitum* access to food (12) and were later designated as *ad libitum*-fed fatties (AF) or *ad libitum*-fed leans (AL). Pups from litters of 18 were fed a daily ration of food equal to the mean amount consumed by the *ad libitum*-fed lean group. The developing obese rats were thus prevented from becoming hyperphagic and were designated as restricted fatties (RF). For the lean rats the daily ration was no longer restrictive and they were desig-

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[4] All rats were fed a semipurified powdered diet as previously discribed (12). The caloric composition was approximately 29% casein, 6% sucrose, 50% starch, and 14% corn oil.

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nated early-restricted leans (ERL). Groups of male rats (n = 4) were killed by decapitation at 15 and 33 weeks of age. Right gastrocnemius muscle, kidneys, brain, and liver were dissected and weighed. RNA was extracted as described by Fleck and Munro (13) and DNA, by the method of Hutchinson (14). Both were quantitated by ultraviolet absorption. Protein content was determined by the colormetric Biuret method (15). All data were analyzed using a two or three way analysis of variance followed by simple effects tests and comparisons of individual means (16).

Results. *Ad libitum*-fed obese rats had eaten more total calories than *ad libitum*-fed leans at both 15 and 33 weeks of age (Table I). Consequently, the fatty group restricted to the *ad libitum* lean daily ration consumed significantly fewer calories than *ad libitum*-fed fatties. Early-restricted lean rats consumed fewer calories than any other group (Table I). At 15 weeks of age, the body weight of the restricted fatties equaled that of the *ad libitum*-fed leans, but became greater than that of the *ad libitum* leans at 33 weeks of age in spite of an identical food intake (Table I). The *ad libitum* fatties weighed significantly more than all other groups at both ages. However despite the decreased body weights the restricted fatties had an absolute amount of fat similar to that of the *ad libitum*-fed fatties (11).

Muscle growth. As has been previously reported (17) muscle weights of the *ad libitum*-fed obese rats are significantly less than those of the *ad libitum*-fed lean rats. This decrease can now be attributed primarily to both decreased DNA and protein (Table II). Impressively, this decrease in DNA and protein is further and significantly accentuated by restricting genetically obese rats to the intake of lean rats. At both 15 and 33 weeks of age the gastrocnemius muscle of the chronically restricted obese rats weighed significantly less than those of the other three groups (Table II). At 15 weeks of age, the muscle weight of the restricted fatties was 70% of the value of *ad libitum*-fed fatties and only 50% of the value for *ad libitum*-fed lean rats. At 33 weeks of age the values were 82 and 47%, respectively. The decrease in muscle weight of the restricted fatty was accompanied by significant decreases in DNA, protein, and RNA compared to all other groups at 15 weeks of age and DNA and protein values were significantly lower compared to all other groups at 33 weeks of age (Table II).

Evaluation of the RNA:DNA and pro-

TABLE I. CUMULATIVE FOOD INTAKE AND BODY WEIGHT OF *AD LIBITUM*-FED AND FOOD-RESTRICTED LEAN AND OBESE ZUCKER RATS AT 15 AND 33 WEEKS OF AGE ($\bar{X}$ ± SEM)

	Cumulative food intake (kcal)		Body weight (g)	
	4–15 weeks	4–33 weeks	15 weeks	33 weeks
AL	5693.38[d] ±200.92	15,739.90[d] ±585.40	325.3 ±6.8	426.0[c,d] ±10.1
AF	7226.00[a,b] ±116.90	19,570.53[a,b] ±488.16	420.0[a,b] ±5.8	633.5[a,b] ±18.4
ERL	5022.80 ±64.35	14,154.80 ±641.70	316.3 ±6.9	359.0 ±16.3
RF	5249.48[c] ±53.93	15,291.50[c] ±209.40	313.0 ±4.5	520.5[c,e] ±15.9

Note. AL = *ad libitum*-fed lean rats; AF = *ad libitum*-fed obese rats; ERL = early food-restricted lean rats; RF = food-restricted obese rats n = 4 for all groups.

[a] AF significantly different from AL.
[b] AF significantly different from RF.
[c] RF significantly different from AL.
[d] AL significantly different from ERL.
[e] RF significantly different from ERL.

TABLE II. GASTROCNEMIUS MUSCLE WEIGHT, DNA, RNA, AND PROTEIN CONTENT AND PROTEIN:DNA IN *AD LIBITUM*-FED AND FOOD-RESTRICTED ZUCKER RATS AT 15 AND 33 WEEKS OF AGE ($\bar{X} \pm$ SEM)

	Weight (g)		Total DNA (mg)		Total RNA (mg)		Total protein (mg)		Protein:DNA		RNA:DNA	
	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks
AL	1.15 ±0.08	1.51[d] ±0.04	0.83 ±0.01	0.74[d] ±0.02	0.59[d] ±0.02	0.50 ±0.00	121.32 ±2.76	124.34 ±1.65	145.40 ±3.09	168.83[d] ±2.67	0.71[d] ±0.02	0.69[d] ±0.01
AF	0.85[a,b] ±0.07	1.05[a,b] ±0.06	0.70[a,b] ±0.06	0.62[a,b] ±0.01	0.35[a,b] ±0.04	0.39[a] ±0.02	86.61[a] ±5.46	104.21[a,b] ±7.91	124.87[b] ±8.65	166.69[b] ±11.35	0.50[a,b] ±0.02	0.62 ±0.03
ERL	1.24 ±0.07	1.32 ±0.08	0.81 ±0.06	0.52 ±0.01	0.49 ±0.03	0.49 ±0.00	113.79 ±5.61	122.11 ±0.57	141.25 ±4.01	233.27 ±2.77	0.60 ±0.01	1.16 ±0.25
RF	0.58[c,e] ±0.02	0.41[c,e] ±0.04	0.86[c,e] ±0.01	0.47[c,e] ±0.02	0.26[c,e] ±0.01	0.38[c,e] ±0.01	83.16[c,e] ±2.87	88.13[c,e] ±2.50	204.70[c,e] ±11.32	187.81[c,e] ±3.51	0.64[c] ±0.01	0.82[c] ±0.01

Note. Right Gastrocnemius muscle was used. AL = *ad libitum*-fed lean rats; AF = *ad libitum*-fed obese rats; ERL = early food-restricted lean rats; RF = food-restricted obese rats. $n = 4$ for all data points.

[a] AF significantly different from AL.
[b] AF significantly different from RF.
[c] RF significantly different from AL.
[d] AL significantly different from ERL.
[e] RF significantly diffeent from ERL.

tein:DNA ratios between the two *ad libitum*-fed groups showed no significant differences except for a decreased RNA:DNA ratio at 15 weeks in the *ad libitum*-fed obese rat compared to the *ad libitum*-fed lean. Restricted fatties had a significantly increased protein:DNA ratio compared to all other groups at 15 weeks of age. At 33 weeks of age, restricted fatties still had a significantly elevated protein:DNA ratio when compared to either *ad libitum* groups but was significantly decreased compared to early-restricted leans. Statistical comparisons for the RNA:DNA at 33 weeks were similar to the protein:DNA values. These data indicate that moderate food restriction decreased cell number in muscle and also altered protein and RNA metabolism.

Kidney growth. At both 15 and 33 weeks of age the kidneys of the restricted fatties weighed significantly less than those of *ad libitum*-fed fatties and at 15 weeks of age the kidneys of the restricted fatties weighed significantly less than those of all three other groups (Table III). The decrease in kidney weights at 15 weeks of age was accompanied by a significant decrease in total DNA per two kidneys in the restricted fatty rats. At 33 weeks of age the restricted fatties still had significantly less DNA than both the *ad libitum*-fed lean and obese rats but significantly more DNA than the early-restricted lean rats. Results for RNA and protein contents of the kidneys paralleled DNA results at both ages although the decrease in the kidney protein and RNA of restricted fatties compared to *ad libitum*-fed lean rats at 33 weeks of age was marginally significant ($0.05 < P < 0.10$) Table III). At 15 weeks of age, there were no differences between any groups in either the protein:DNA or RNA:DNA ratios in the kidneys. At 33 weeks of age, the restricted fatties had a significantly decreased protein:RNA ratio compared to early-restricted lean rats but similar to both *ad libitum*-fed groups. The RNA:DNA ratio of the restricted fatties was decreased compared to all other groups but was only significantly decreased compared to *ad libitum*-fed lean rats.

Brain growth. At both 15 and 33 weeks of

TABLE III. KIDNEY* WEIGHT, DNA, RNA, AND PROTEIN CONTENT AND PROTEIN:DNA IN *AD LIBITUM*-FED AND FOOD-RESTRICTED ZUCKER RATS AT 15 AND 33 WEEKS OF AGE ($\bar{X} \pm$ SEM)

	Weight (g)		Total DNA (mg)		Total RNA (mg)		Total protein (mg)		Protein:DNA		RNA:DNA	
	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks
AL	2.08 ±0.06	2.48[d] ±0.10	7.14 ±0.02	5.22[d] ±0.08	7.17 ±0.36	6.37[d] ±0.21	248.34 ±6.02	200.00[d] ±8.09	34.79 ±0.77	38.30[d] ±0.98	1.00 ±0.05	1.22 ±0.04
AF	2.13[a,b] ±0.08	2.72[a,b] ±0.09	7.00[b] ±0.45	5.66[a,b] ±0.10	7.38[b] ±0.37	6.37[b] ±0.17	235.00[b] ±2.68	221.05[b] ±5.23	33.90 ±1.77	39.04 ±0.77	1.06 ±0.04	1.12 ±0.03
ERL	2.14 ±0.09	2.18 ±0.21	7.30 ±0.06	3.94 ±0.17	7.43 ±0.22	4.65 ±0.30	258.67 ±15.42	172.70 ±9.31	35.41 ±1.93	43.85 ±1.23	1.02 ±0.02	1.18 ±0.05
RF	1.55[c,d] ±0.05	2.25[c] ±0.03	5.53[c,d] ±0.15	4.53[c,d] ±0.06	5.57[c,d] ±0.21	4.95[c] ±0.03	178.67[c,d] ±3.26	181.91 ±2.96	32.36 ±0.35	40.15[c] ±0.89	1.01 ±0.03	1.09[c] ±0.01

Note. Both kidneys were used. AL = *ad libitum*-fed lean rats; AF = *ad libitum*-fed obese rats; ERL = early food-restricted lean rats; RF = food-restricted obese rats. $n = 4$ for all data points.

[a] AF significantly different from AL.
[b] AF significantly different from RF.
[c] RF significantly different from AL.
[d] AL significantly different from ERL.
[e] RF significantly different from ERL.

age overall brain growth of restricted fatties was less affected than muscle, kidney, or liver. However, at 15 and 33 weeks of age brain weights of the restricted obese rats were less than both *ad libitum*-fed and early-restricted leans, and in addition at 15 weeks the brains of the restricted fatties weighed less than the *ad libitum*-fed fatties (Table IV). Furthermore, at both ages the brains of the *ad libitum* fatties weighed less than those of the *ad libitum*-fed leans but this difference was only significant at 15 weeks of age. Nonetheless, despite the decreased brain weights of both groups of obese rats, the total DNA content of their brains was moderately but significantly greater than that of the lean rats at 15 weeks of age. At 33 weeks of age, the brain DNA of the restricted fatty rats was significantly greater than that of the *ad libitum*-fed fatties and leans but was less than the total brain DNA of the early-restricted leans. There were no differences in brain RNA content at 15 weeks of age between groups but at 33 weeks of age brain RNA of the early-restricted leans was significantly elevated. At 15 weeks of age brain protein was decreased in both obese groups compared to both lean groups, while at 33 weeks of age only the restricted fatties had significantly decreased values.

At 15 weeks of age both groups of obese rats had decreased RNA:DNA and protein:DNA ratios compared to the lean groups. By 33 weeks, however, only the restricted fatties had a significantly decreased protein:DNA ratio compared to both lean groups. The RNA:DNA ratio was significantly decreased in the restricted fatties compared to *ad libitum*-fed lean rats. The *ad libitum*-fed lean and obese and early-restricted leans all had a similar RNA:DNA ratio.

Liver growth. As has been previously reported by other investigators, the livers from *ad libitum*-fed fatties at both 15 and 33 weeks of age were significantly heavier than those of lean rats (Table V). In this study, the tendency to increase liver weight was also present in the restricted fatty group which had liver weights significantly greater than those of both lean groups by 33 weeks of age. However, the restricted fat-

TABLE IV. BRAIN WEIGHT, DNA, RNA, AND PROTEIN CONTENT AND PROTEIN:DNA IN *AD LIBITUM*-FED AND FOOD-RESTRICTED ZUCKER RATS AT 15 AND 33 WEEKS OF AGE ($\bar{X}$ ± SEM)

	Weight (g)		Total DNA (mg)		Total RNA (mg)		Total protein (mg)		Protein:DNA		RNA:DNA	
	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks
AL	1.86 ±0.05	1.98 ±0.04	2.63 ±0.14	2.46[d] ±0.01	2.47 ±0.05	2.31 ±0.06	136.32 ±1.78	134.42 ±3.76	52.35 ±3.27	54.24[d] ±1.84	0.95 ±0.04	0.94 ±0.02
AF	1.69[a] ±0.03	1.86 ±0.02	3.11[a] ±0.06	2.60[b] ±0.06	2.50 ±0.07	2.31 ±0.08	127.69[a] ±2.12	131.37 ±1.88	41.15[a] ±1.13	50.73 ±2.48	0.80[a] ±0.02	0.89 ±0.04
ERL	1.93 ±0.02	1.92 ±0.03	2.56 ±0.08	2.87 ±0.10	2.42 ±0.08	2.60 ±0.05	135.26 ±1.76	136.67 ±4.11	52.96 ±1.41	46.30 ±0.74	0.95 ±0.03	0.91 ±0.02
RF	1.62[c,e] ±0.03	1.74[c,e] ±0.04	2.87[c] ±0.08	2.93[c] ±0.07	2.42 ±0.05	2.29 ±0.02	124.08[c,e] ±4.49	116.79[c] ±3.66	43.21[c,e] ±1.52	39.82[c,e] ±1.63	0.84[c] ±0.01	0.78[c] ±0.02

Note. AL = *ad libitum*-fed lean rats; AF = *ad libitum*-fed obese rats; ERL = early food-restricted lean rats; RF = food-restricted obese rats. $n = 4$ for all data points except 33-week-old RF where $n = 2$.

[a] AF significantly different from AL.
[b] AF significantly different from RF.
[c] RF significantly differetn from AL.
[d] AL significantly different from ERL.
[e] RF significantly different from ERL.

TABLE V. LIVER WEIGHT, DNA RNA, AND PROTEIN CONTENT AND PROTEIN:DNA IN *AD LIBITUM*-FED AND FOOD-RESTRICTED ZUCKER RATS AT 15 AND 33 WEEKS OF AGE ($\bar{X}$ ± SEM)

	Weight (g)		Total DNA (mg)		Total RNA (mg)		Total protein (mg)		Protein:DNA		RNA:DNA	
	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks	15 weeks	33 weeks
AL	10.07 ±0.44	12.28 ±0.49	18.10 ±0.17	18.78 ±1.01	62.06 ±1.65	59.18 ±0.81	1168.42[d] ±41.88	915.13 ±70.40	64.54[d] ±2.14	50.87 ±2.99	3.43[d] ±0.11	3.18 ±0.16
AF	14.03[a,b] ±0.03	18.08[a,b] ±1.23	18.91[b] ±1.44	20.19 ±1.40	70.99[b] ±3.42	77.81[a,b] ±5.62	1475.13[a,b] ±125.20	1587.23[a,b] ±186.81	78.18[a] ±3.69	77.89[a,b] ±3.84	3.78[a] ±0.13	3.85[a] ±0.02
ERL	9.77 ±0.78	11.00 ±0.53	19.94 ±0.65	15.64 ±0.69	59.87 ±3.72	54.26 ±3.15	849.89 ±5.84	784.47 ±87.07	42.74 ±1.27	49.74 ±3.47	2.99 ±0.10	3.46 ±0.05
RF	11.17 ±0.21	14.78[c,e] ±0.43	15.07[c,e] ±0.68	17.14 ±1.09	60.24 ±3.93	72.84 ±4.76	1160.79[c] ±42.12	1104.21 ±56.82	77.13[c,e] ±1.21	64.72[c,e] ±2.40	3.99[c,e] ±0.27	4.28[c,e] ±0.25

Note. AL = *ad libitum*-fed lean rats; AF = *ad libitum*-fed obese rats; ERL = early food-restricted lean rats; RF = food-restricted obese rats. $n = 4$ for all data points.

[a] AF significantly different from AL.
[b] AF significantly different from RF.
[c] RF significantly different from AL.
[d] AL significantly different from ERL.
[e] RF significantly different from ERL.

ties had less liver DNA than all other groups at both 15 and 33 weeks of age but the value was significantly lower only at 15 weeks of age. The liver RNA content of restricted fatties was significantly decreased at 15 weeks of age compared to *ad libitum*-fed fatties but at 33 weeks of age there was no longer a significant difference between the two groups. Protein content per liver was significantly greater for *ad libitum*-fed fatties at both 15 and 33 weeks of age compared to all other groups. No significant differences in liver protein content were found at either age between the restricted fatties and either of the lean groups.

In general, both the RNA:DNA and protein:DNA ratios were higher in the obese rats regardless of dietary treatment. This may reflect the increased lipogenic activity seen in both the *ad libitum*-fed and food-restricted obese rats (11).

Discussion. The etiology of hyperplastic-hypertrophic obesity in the Zucker rat has not been established. Hyperphagia is one of the earliest alterations observed (18) but prevention of preweaning hyperphagia by increasing litter size did not prevent the subsequent development of obesity (6). Numerous studies of postweaning food restriction have also shown that the genetically obese rat will remain obese, laying down adipose tissue at the expense of lean body mass (9, 17, 19, 21). In addition we have previously reported that obese rats, food restricted at both pre- and postweaning, have essentially the same amount of body fat (in grams) at 33 weeks of age as *ad libitum*-fed obese rats (11). These restricted obese rats also had hyperplastic-hypertrophic adipose depots. Thus hyperphagia clearly does not appear to be the primary defect in this form of obesity.

The results from the present study further indicate that the hyperphagia seen in the *ad libitum*-fed obese rat did not lead to increased cell number of organs other than adipose tissue. This is in contrast to results found in other strains of rats (22, 23). In fact *ad libitum*-fed obese rats have been shown to have decreased muscle mass when compared to *ad libitum*-fed lean rats in this and several previous studies (17, 24). The data presented here and in a recent study (24) indicate that the smaller muscle mass is due to a decrease in muscle cell number. In both studies food restriction further compromised muscle cellular growth.

There are several possible explanations for the alteration of muscle growth found in the obese Zucker rat and the additional effect of food restriction. We have previously hypothesized that the decreased muscle growth is due at least in part to a diversion of circulating substrate into adipose tissue even when caloric intake is restricted (11). In addition it appears that the *ad libitum*-fed obese rat utilizes and lays down less dietary protein compared to the lean rat (25, 26). This occurs in the presence of insulin resistance of the muscle tissue in the obese rat (27, 29). The food-restricted obese rats in this study were found to have serum insulin levels significantly elevated compared to the *ad libitum*-fed obese rats (11). This might lead to a further exacerbation of the insulin resistance in muscle tissue in the food-restricted obese rats, which may result in a further decrease in the ability of the muscle cells of these rats to utilize protein.

Another possible explanation for the decreased muscle growth in the obese rat may be related to abnormalities in growth hormone. Zucker speculated that a deficiency of this hormone is present in the obese rat (7) and Martin and co-workers have shown that obese Zucker rats have serum growth hormone levels lower than those of leans (8, 30). Furthermore, obese Zucker rats have been shown to decrease serum hormone levels during a fast while lean rats maintained their growth hormone levels (30). Although growth hormone levels have not been determined during chronic food restriction, supplementation of growth hormone to food-restricted obese rats resulted in increased muscle mass (7). Thus food restriction may be further altering growth hormone metabolism leading to a greater effect on the already compromised muscle growth found in the obese Zucker rat.

Increased liver weight was found in *ad libitum*-fed obese Zucker rat in this and previous studies (7, 31–33). The increased

weight has been attributed to fatty infiltration (31). However, our results indicate that some of this increased weight is due to the substantially increased protein:DNA and RNA:DNA ratios (Table V). These results are in agreement with Zucker's previous observation that the amount of fatty infiltration was not sufficient to account for the enlarged livers (7). DNA per total liver was not found to be increased in the hyperphagic *ad libitum*-fed obese rats compared to lean controls. Food restriction did significantly decrease total DNA in livers of the restricted obese rats at 15 weeks of age but apparently the restricted obese rat restored the value to normal at 33 weeks of age. The food-restricted obese rats had a protein:DNA ratio similar to that of the *ad libitum*-fed obese rats. Consequently, the long-term effect of food restriction on hyperplastic growth appears less permanent in the liver than in muscle tissue. It has also been previously reported that food restriction does not appear to substantially decrease the hyperlipogenesis characteristic of the livers of the obese rats (11).

Kidneys of *ad libitum*-fed obese rats have increased rates of gluconegenesis compared to lean rats (34). The effect of the decrease in kidney DNA reported here on kidney metabolism remains to be investigated. However, the effects of food restriction on kidney growth and metabolism may be of great importance, as rats in general tend to develop glomerulonephritis with age (35) and Zucker rats seem to be prematurely affected (36). Postweaning food restriction has been shown to increase longevity and delay the development of glomerulonephritis in rats (37) and to increase the life span of the Zucker rat (38). However, the consequences of both pre- and postweaning food restriction on kidney metabolism and morbidity remain to be investigated.

In general these results indicate that moderate chronic food restriction in the obese Zucker rat can compromise the growth of some tissues. The long-term effects of these alterations on such factors as physiological function and life span remain to be investigated. However, the fact that an obese body composition is maintained in these rats (11) indicated no amelioration of this well-known risk factor for premature morbidity and mortality. If the hyperplastic-hypertrophic form of human obesity responds to early dietary interventions in a similar manner, treatments other than simple caloric restriction must be sought.

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