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Dietary Induction of Hepatic Glucose-6-phosphate Dehydrogenase, 6-Phosphogluconate Dehydrogenase, and Malic Enzyme in Lean and Obese Female Zucker Rats (42479)

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Abstract. Responses of the hepatic lipogenic enzymes, glucose-6-phosphate dehydrogenase (G6PDH), 6-phosphogluconate dehydrogenase (6PGDH), and malic enzyme (ME) to starvation refeeding and diet shifting were determined in lean and obese female Zucker rats. Rats were either (i) fed nonpurified diet, starved 48 hr, and then refed nonpurified diet or one of the refined carbohydrate diets containing either glucose, fructose, cornstarch, or sucrose for 72 hr, or (ii) shifted from nonpurified diet directly to one of the refined carbohydrate diets for 72 hr. Initial activities were greater in obese than lean rats for all three enzymes studied. Similar to other strains of female rats, lean Zucker rats failed to demonstrate a starve–refeed response when refed nonpurified diet. Obese female littermates showed a statistically significant increase in enzymes when refed a nonpurified diet. Both lean and obese female Zucker rats demonstrated increases in enzyme activities above controls when starved and refed any of the refined carbohydrate diets. The greatest responses were observed when female rats were starved and refed sucrose; activities increased 2.6- to 3.5-fold in lean and 3.0- to 4.3-fold in obese Zuckers. In lean females 50–70% of the starve–refeed response observed with G6PDH and ME can be accounted for by simply shifting from a nonpurified diet to the respective refined carbohydrate diet, whereas in obese females only 33–55% of the increase could be attributed to diet shifting. Plasma testosterone/estrogen ratios were consistently 1.5 times higher in obese than in lean female rats. This phenotypic difference may potentiate the heightened starve–refeed overshoot response observed in obese rats.

Epidemiological studies have correlated excessive consumption of refined carbohydrates, particularly sucrose, with escalating rates of human obesity, diabetes, and cardiovascular disease (1). Likewise, sucrose-rich diets have been reported to increase lipogenesis and obesity in laboratory rodents (2).

Increased hepatic lipogenic enzyme activities appear to be important in the development of liver steatosis and excessive body fat, both in genetic and environmental obesity (3–6). Rat hepatic glucose-6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase (6PGDH) have been shown to be highly susceptible to dietary alterations. Numerous studies have demonstrated that simply shifting rats from a complex carbohydrate commercial diet to a refined carbohydrate source significantly increases G6PDH and 6PGDH activities (8, 10, 11). This stimulatory effect is further accentuated when rats are fed a purified high-carbohydrate, low-fat diet subsequent to a period of starvation.

A limited number of studies have investigated the lipogenic response of male Zucker rats shifted to diets containing high percentages of refined carbohydrates (6, 12). Without an intervening period of starvation hepatic lipogenic enzymes of male lean and fatty Zucker rats appear to be equally susceptible to induction by refined dietary carbohydrate, although absolute basal and final enzyme levels are different in the lean and obese littermates.

Several studies have shown that sex hormones modify the activities of G6PDH, 6PGDH, and malic enzyme (ME) (13–15). As weanlings, males and females have equivalent levels of these enzymes; following puberty activities double in female rats but remain unaltered in males (13, 14). Recent research in this laboratory has revealed that not only are the basal levels of these enzymes influenced by gender, the susceptibility of these enzymes to induction by dietary alterations also is gender dependent (8). Although young adult female Sprague–Dawley rats have twice the enzyme activity of age-matched males, their

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starve–refeed overshoot response is 75% of that observed in males. Further analysis of the data demonstrated that a high estrogen/testosterone ratio increased basal enzyme activities whereas an elevated testosterone/estrogen ratio amplified responsiveness to starvation refeeding.

The role of sex hormones in determining basal hepatic lipogenic enzyme activities, our observations that enzyme activities are altered by an animal's estrogen/testosterone ratio, and reports of secondary amenorrhea and oligomenorrhea (16, 17) induced by peripheral conversion of testosterone to estrogen in adipose tissue of obese human females prompted this study. The main aim was to determine if genetically dictated obesity as typified by Zucker rats modifies the normally attenuated overshoot response of adult female rats.

Materials and Methods. *Animals.* Littermate pairs of 5-week-old lean and obese female Zucker rats were obtained from the campus breeding colony (Dr. Judith Stern, Department of Nutrition, University of California, Davis, CA). Rats were individually housed in wire mesh cages at 27°C with alternating 12-hr light and dark cycles and free access to food and water. Animals were permitted to equilibrate to their new environment for 2 weeks before initiation of an experiment.

Chemicals. Substrates for glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and malic enzyme assays were obtained from Sigma Chemical Co. (St. Louis, MO). Constituents of the purified carbohydrate diets were purchased from Nutritional Biochemicals, Inc. (Cleveland, OH) with the exception of Mazola corn oil, which was obtained locally.

Dietary treatments. During the equilibration period all rats were fed a finely ground commercial diet (Purina Lab Chow: 66% carbohydrate, 23% protein, 4.5% fat, 8% ash, 3% added mineral and vitamin supplements) for 5 days. Rats in the control groups for each experiment continued to receive this diet throughout each experiment.

Experimental animals were fed purified diets containing 65% carbohydrate (either glucose, sucrose, fructose, or cornstarch), 25% casein, 5% Mazola corn oil, 4% Rogers & Harper salt mix corrected for Cr ($CrK(SO_4)_2 \cdot 12H_2O$, 15.45 mg/kg diet), Zn ($ZnCl_2$, 24 mg/kg diet), Mn ($MnSO_4 \cdot H_2O$, 145 mg/kg diet), Fl (NaF, 1.8 mg/kg diet), and 1% AIN-76A vitamin mix.

In the starvation–refeeding study rats were maintained on ground commercial diet until the starvation period. Following 2 days of starvation, pairs of randomly selected lean and obese littermates were refed one of the purified diets or ground commercial diet for 3 days *ad libitum.*

To assess the impact on enzyme activities of shifting rats from a nonpurified diet to a purified ration, a second group of littermates were prefed ground commercial diet and then switched directly to one of the refined carbohydrate diets for 3 days. Food intake and body weights were recorded between 8:00 and 9:00 AM daily for all rats. At the end of the studies rats were anesthetized with pentobarbital (6.5 mg/100 g body wt), a vaginal cytology slide was prepared, and then the rats were decapitated and exsanguinated. Serum separated from blood obtained at the time of death was assayed for estradiol and testosterone by the methods of Shille *et al.* (18) and Stabenfeldt *et al.* (19), respectively.

Livers were removed rapidly, weighed, and chilled. A 0.5-g portion of the median lobe was homogenized in 4.5 ml ice-cold Tris–KCl buffer with mercaptoethanol (10). Homogenate (200 μl) was removed for determination of DNA content as described by Burton (20). The remainder was centrifuged at 4°C and 30,000*g* for 30 min. Enzyme activities were measured in the resulting clear infranates using sample volumes which kept the reaction in the linear range of each assay. G6PDH and 6PGDH activities were assayed as described by Glock and McLean (21) and modified by Kagawa *et al.* (22). Malic enzyme was assayed by the method of Wise and Ball (23). When equal volumes of liver infranate from normal and from obese rats were mixed and assayed, it was determined that the enzyme activities were additive one to the other. This would indicate that neither inhibitory nor stimulatory factors were present in either infranate.

Enzyme activities are expressed per milligram of DNA because DNA per liver, in contrast to liver weight or liver protein, is unchanged by starvation–refeeding.

Statistics. Data were statistically analyzed using two-way analysis of variance with a matched-pair response. Grouping factors

consisted of the prefeed (starvation or commercial nonpurfied diet) and refeed (refed or diet shifted) treatments. The effect of genotype also was assessed as animals in each of the above groups were matched pairs (lean and obese) obtained from the same litter. Means for each genotype (lean, obese), as well as mean differences, were compared using the Bonferroni multiple-comparison method following two-way analysis of variance (24).

Results. *Weight gain.* Obese Zucker rats gained an average of 2.5 g/day when fed commercial diet as compared to 1.5 g/day gained by their lean siblings. During the refeeding phase of the starve–refeed study both genotypes of rats gained from 7 to 10 g/day irrespective of diet. When shifted directly from commercial nonpurified diet to purified carbohydrate diets obese rats gained almost 3 g and lean rats 2.5 g/day (Table I).

Food intake. In both studies, obese Zucker rats consumed more food on a gram per day basis than their lean siblings. Food consumption ranged from 13.2 to 15.8 g/day in obese and from 7.8 to 9.8 g/day in lean rats. Intake was slightly higher during the refeeding phase of the starve–refeed regime in both phenotypes. When food intake was corrected for metabolic body size (g food consumed/(body wt)$^{\frac{2}{3}}$) (25) no significant differences in food in-

TABLE I

	Final body wt (g)	Wt gain (g/day)	Food intake		RLS (g liver/100 g body wt)	EST (pg/ml plasma)	TEST (pg/ml plasma)
			g/day	g/day/body wt$^{2/3}$			
Starve–refeed							
Lean							
NP	142 ± 15	1.5 ± 0.5	9.8 ± 0.7	0.37 ± 0.03	4.1 ± 0.3[a]	29 ± 7	56 ± 3
Starve	109 ± 4	—	—	—	2.5 ± 0.2	18 ± 8	66 ± 30
Refed							
NP	130 ± 5	9.0 ± 0.7	10.5 ± 1.0	0.42 ± 0.04	4.3 ± 0.1[a]	17 ± 6	60 ± 19
Starch	134 ± 5	8.1 ± 0.6	11.2 ± 1.2	0.44 ± 0.04	4.0 ± 0.1[a]	13 ± 7	74 ± 8
Glucose	121 ± 7	7.8 ± 0.5	11.4 ± 1.0	0.46 ± 0.05	4.6 ± 0.4[a]	21 ± 8	59 ± 14
Fructose	127 ± 3	7.5 ± 1.0	12.8 ± 1.3	0.52 ± 0.06	6.1 ± 0.3[b]	25 ± 8	43 ± 17
Sucrose	131 ± 3	8.9 ± 0.4	13.6 ± 1.5	0.54 ± 0.04	6.5 ± 0.3[b]	18 ± 4	57 ± 3
Obese							
NP	178 ± 11	2.5 ± 0.4	13.8 ± 1.5	0.45 ± 0.05	4.1 ± 0.31[a]	15 ± 2	83 ± 5
Starve	133 ± 11	—	—	—	2.4 ± 0.16	11 ± 1	64 ± 6
Refed							
NP	142 ± 9	8.9 ± 0.8	12.6 ± 1.2	0.48 ± 0.05	4.7 ± 0.6[a]	12 ± 2	78 ± 5
Starch	139 ± 5	8.3 ± 0.4	14.0 ± 1.5	0.54 ± 0.06	4.0 ± 0.7[a]	11 ± 2	71 ± 6
Glucose	146 ± 5	10.3 ± 1.3	14.5 ± 1.3	0.56 ± 0.06	4.5 ± 0.3[a]	16 ± 3	74 ± 6
Fructose	149 ± 3	8.8 ± 0.7	12.8 ± 1.0	0.53 ± 0.05	6.2 ± 0.3[b]	15 ± 2	88 ± 8
Sucrose	156 ± 11	7.2 ± 0.5	14.5 ± 1.6	0.52 ± 0.06	6.3 ± 0.6[b]	12 ± 2	69 ± 6
Diet shift							
Lean							
NP	142 ± 9	1.5 ± 0.5	9.8 ± 0.7	0.37 ± 0.03	4.1 ± 0.3	29 ± 7	56 ± 3
Starch	142 ± 7	2.1 ± 0.3	9.7 ± 0.7	0.36 ± 0.04	3.6 ± 0.3	19 ± 6	60 ± 4
Glucose	138 ± 8	2.2 ± 0.4	8.9 ± 1.0	0.34 ± 0.04	3.8 ± 0.3	17 ± 4	45 ± 6
Fructose	133 ± 8	2.6 ± 0.4	7.8 ± 1.1	0.32 ± 0.05	4.8 ± 0.3	22 ± 8	52 ± 5
Sucrose	147 ± 10	2.8 ± 0.5	9.8 ± 1.3	0.36 ± 0.05	5.0 ± 0.2	20 ± 10	63 ± 7
Obese							
NP	178 ± 11	2.6 ± 0.6	13.8 ± 1.5	0.45 ± 0.05	4.1 ± 0.3	15 ± 2	83 ± 5
Starch	198 ± 10	3.4 ± 0.5	13.7 ± 0.9	0.42 ± 0.03	4.2 ± 0.38	14 ± 1	73 ± 6
Glucose	183 ± 9	2.7 ± 0.6	13.5 ± 1.6	0.44 ± 0.05	3.9 ± 0.41	16 ± 1	77 ± 5
Fructose	186 ± 10	3.1 ± 0.7	13.2 ± 1.1	0.43 ± 0.06	5.3 ± 0.44	16 ± 2	80 ± 6
Sucrose	195 ± 13	2.9 ± 0.7	15.8 ± 1.4	0.48 ± 0.05	5.7 ± 0.56	13 ± 2	82 ± 5

[a,b] Differences between diets within a given genotype. *Note.* Values are means for three rats ± SEM. Those values not sharing a common superscript differ significantly by $P < 0.05$. RLS, relative liver size; EST, estrogen, TEST, testosterone, NP, commercial nonpurified diet. Data on starved rats are presented for comparative purposes only.

take were noted between diets or genotypes within an experiment (Table I).

Relative liver size. Regardless of the feeding regime, absolute liver weights were highest in obese rats consuming purified diets: 9.7 g for obese rats as compared to 7.4 g for lean rats similarly fed. However, when liver weight was expressed as grams of liver per 100 grams body weight (relative liver size) these differences tended to be self correcting so that relative liver size (RLS) did not differ between genotypes within a given diet treatment. Significant diet effects on RLS were seen in rats fed the fructose or sucrose diets in the starve–refeed study. In these rats RLS was significantly greater than in rats refed the nonpurified diet, starch, or glucose (Table I).

Hepatic enzyme activity. Basal activity levels of hepatic G6PDH, 6PGDH, and ME were significantly higher (17%) in obese than in lean Zucker rats fed commercial diet (Tables II and III). In general, obese Zucker rats tended to respond more to starvation–refeeding than their lean littermates. Hepatic enzyme activities in lean female Zuckers following starvation and refeeding of commercial diet were identical to prestarvation activities, whereas obese rats refed commercial diet manifested 1.3-fold increases in G6PDH and ME, and 1.7-fold increases in 6PGDH activities. Hepatic enzyme activities rose 2.5–3 times in rats starved and refed starch or glucose, and 3.5 times in those refed fructose. Of the purified carbohydrates tested, sucrose was the most potent stimulator of enzyme activities, increasing G6PDH activity 3.4- and 4.3-fold in lean and obese rats, respectively (Table II). There was a significant interaction between feeding regime and genotype on enzyme activity of rats in the starve–refeed study. Obese rats had statistically greater hepatic enzyme activities with each diet tested than did their lean littermates.

Lean and obese rats were equally sensitive to shifts in dietary carbohydrate source. When lean rats were shifted from nonpurified commercial diet directly to a refined carbohydrate diet, their hepatic enzyme activities increased 1.5–2.3 times (Table III). Obese rats similarly treated had 1.8- to 2.5-fold increases in enzyme activity (Table III). As in the starve–refeed studies, rats were increasingly responsive to starch, glucose, fructose, and sucrose (Table III). Significant genotype differences in enzymatic response during the diet shift experiment were noted only in rats consuming sucrose. In this instance obese Zucker rats had significantly greater enzyme activity (Table III).

TABLE II. HEPATIC G6PDH, 6PGDH, AND ME ACTIVITIES $\left(\frac{\text{units}}{\text{mg/DNA}}\right)$ OF ADULT FEMALE ZUCKER RATS STARVED AND REFED REFINED CARBOHYDRATES

	G6PDH		6PGDH		ME	
	Lean	Obese	Lean	Obese	Lean	Obese
Diet group						
NP controls	$^{x}3.2 \pm 0.14^{a}$	$^{y}3.8 \pm 0.21^{a}$	$^{x}3.31 \pm 0.19^{a}$	$^{y}4.05 \pm 0.23^{a}$	$^{x}2.14 \pm 0.11^{a}$	$^{y}2.99 \pm 0.13^{a}$
Starve	1.24 ± 0.10	1.53 ± 0.09	1.79 ± 0.11	1.95 ± 0.15	1.01 ± 0.08	1.68 ± 0.12
Refeed						
NP	$^{x}2.78 \pm 0.23^{a}$	$^{y}4.69 \pm 0.35^{b}$	$^{x}3.70 \pm 0.25^{a}$	$^{y}6.76 \pm 0.42^{b}$	$^{x}2.33 \pm 0.20^{a}$	$^{y}3.69 \pm 0.28^{b}$
Starch	$^{x}8.94 \pm 0.5^{b,c}$	$^{y}11.16 \pm 0.67^{c}$	$^{x}8.85 \pm 0.50^{b}$	$^{y}9.55 \pm 0.50^{c}$	$^{x}6.43 \pm 0.55^{b}$	$^{y}8.79 \pm 0.68^{c}$
Glucose	$^{x}8.10 \pm 0.50^{b}$	$^{y}11.81 \pm 0.72^{c}$	$^{x}8.12 \pm 0.53^{b}$	$^{y}9.81 \pm 0.68^{c}$	$^{x}6.98 \pm 0.71^{b}$	$^{y}9.46 \pm 0.73^{c}$
Fructose	$^{x}9.54 \pm 0.61^{c}$	$^{y}13.21 \pm 0.89^{c}$	$^{x}9.15 \pm 0.61^{b}$	$^{y}10.48 \pm 0.62^{c}$	$^{x}7.40 \pm 0.64^{b}$	$^{y}10.35 \pm 0.84^{c}$
Sucrose	$^{x}11.07 \pm 0.64^{d}$	$^{y}16.06 \pm 1.20^{d}$	$^{x}9.73 \pm 0.53^{b}$	$^{y}14.48 \pm 0.83^{d}$	$^{x}8.08 \pm 0.75^{b}$	$^{y}13.09 \pm 1.20^{d}$

$^{a-d}$ Differences between diets within a given genotype.

^{x,y} Differences between genotypes within a given diet.

Note. NP commercial nonpurified diet. Values are means for three rats ± SEM; those values not sharing a common superscript differ significantly by $P < 0.05$. Data on starved rats are provided for comparative purposes only. 1 unit of enzyme activity = formation of 1 μmole of NADPH per minute. Enzyme activity per supernate volume $= \frac{\text{change in OD}}{6.22} \times \frac{\text{total assay volume}}{\text{volume of supernate used}}$.

TABLE III. EFFECTS OF DIET SHIFTING ON HEPATIC G6PDH, 6PGDH, AND ME ACTIVITIES $\left(\frac{\text{units}}{\text{mg/DNA}}\right)$ IN LEAN AND OBESE FEMALE ZUCKER RATS

	G6PDH		6PGDH		ME	
Diet group	Lean	Obese	Lean	Obese	Lean	Obese
NP controls	3.2 ± 0.14^{a}	3.8 ± 0.21^{a}	$^{x}3.4 \pm 0.19^{a}$	$^{y}4.08 \pm 0.24^{a}$	$^{x}2.14 \pm 0.11^{a}$	$^{y}2.99 \pm 0.13^{a}$
Starch	5.27 ± 0.31^{b}	6.27 ± 0.46^{b}	5.83 ± 0.29^{b}	6.95 ± 0.40^{b}	$^{x}3.95 \pm 0.33^{b}$	$^{y}5.03 \pm 0.57^{b}$
Glucose	6.37 ± 0.26^{c}	6.98 ± 0.37^{b}	7.05 ± 0.24^{c}	$7.94 \pm 0.42^{b,c}$	4.71 ± 0.38^{b}	5.65 ± 0.35^{b}
Fructose	7.09 ± 0.36^{c}	8.05 ± 0.39^{c}	$7.51 \pm 0.38^{c,d}$	8.42 ± 0.41^{c}	5.09 ± 0.32^{b}	6.32 ± 0.41^{b}
Sucrose	$^{x}8.63 \pm 0.41^{d}$	$^{y}9.88 \pm 0.46^{d}$	$^{x}7.99 \pm 0.39^{d}$	$^{y}9.39 \pm 0.43^{c}$	$^{x}5.94 \pm 0.40^{c}$	$^{y}7.89 \pm 0.52^{c}$

$^{a-d}$ Differences between diets within a given genotype.

^{x,y} Differences between genotypes within a given diet.

NP, commercial nonpurified diet. Values are means for three rats ± SEM; those values not sharing a common superscript differ significantly by $P < 0.05$. 1 unit of enzyme activity = formation of 1 μmole of NADPH per minute.

Sex hormones. Plasma estradiol levels in lean female Zucker rats ranged from 9 to 40 pg/ml with an average of 19 ± 5 pg/ml reflecting normal estrous cycling (26). The average plasma testosterone level in these rats was 57 ± 2 pg/ml. Estradiol levels in obese Zucker rats were not significantly different from those of their lean siblings, averaging 14 ± 4 pg/ml; however, the range in values was much narrower, suggesting alterations in estrous cycling. Furthermore, plasma testosterone in fatty females was significantly elevated, averaging 76 ± 2 pg/ml. These alterations in testosterone levels translate into higher testosterone/estrogen ratios for obese (5.4) versus lean (3.1) female rats (Table I).

Discussion. The characteristic hyperphagia and decreased estrogen/testosterone ratio of the obese Zucker rat may be partly responsible for their elevated G6PDH, 6PGDH, and ME levels as well as their heightened starve–refeed response. Although hyperphagia develops secondary to obesity (5), it may promote and sustain increased levels of hepatic lipogenic enzymes by maintaining a greater flow of substrate through lipogenic pathways. However, two lines of evidence suggest that the elevation in enzyme activities found in obese rats is not due solely to increased food consumption.

In the present studies, obese rats consumed significantly more food on a gram per day basis than their lean siblings, regardless of the diet. However, expressing food or energy intake on the basis of metabolic body size (body $wt^{\frac{3}{4}}$) obliterated the phenotypic difference in food consumption. Furthermore, studies by others (4) employing a pair-feeding technique which chronologically and quantitatively superimposed the feeding habits of lean Zuckers onto their obese siblings failed to negate certain metabolic anomalies such as hyperlipemia, hypertriglyceridemia, and liver steatosis which previously had been attributed to hyperphagia. These findings were consistent and independent of the dietary carbohydrate source used. Cumulatively, these results indicate that endogenous metabolic factors other than hyperphagia contribute to the greater hepatic lipogenic enzyme activities of fatty Zucker rats.

Obese Zucker rats inherit corpulence as an autosomal recessive trait. Rats used in these studies were obtained by breeding heterozygote recessive parents, which yielded three genotypes but only two phenotypes: (i) homozygous obese (*fa/fa*), (ii) homozygous lean (*Fa/Fa*), and (iii) heterozygous lean (*Fa/fa*). Although the genetic makeup of the lean rats was unknown (and follow-up matings to determine their genotype were not performed), its impact on hepatic enzymatic response must be considered. Two factors indicate that it had little effect: (i) No great variation in measurements was observed for a given parameter within any of the lean treatment groups, and (ii) the absolute enzyme activities and percentage induction achieved with dietary alterations in the lean female Zucker rat were analogous to those found in Sprague–Dawley females which are homozygous lean.

The elevated testosterone/estrogen ratio

observed in obese female Zucker rats appears to have had a significant impact on the susceptibility of their hepatic lipogenic enzymes to induction by dietary alterations. In contrast to lean female Zucker and Sprague–Dawley rats (8) which did not manifest an overshoot response when starved and refed nonpurified diet, obese female Zuckers, like male Sprague–Dawleys, exhibited three- to fourfold increases in enzyme activity. When refed purified carbohydrate diets the enzymatic response of lean female Zuckers was similar to that of female Sprague–Dawleys whereas the response of obese females was intermediate between that of lean females and males.

A previous study in this laboratory demonstrated the importance of partitioning the increase in enzyme activity observed during the refeeding phase of starve–refeed experiments into a true refeed overshoot component and a dietary shift component (enzyme activity after refeeding − enzyme activity after diet shift) (8). The most important difference between phenotypes lies in their overshoot response. Assessing the data in Tables II and III, it is apparent that 50–70% ((enzyme activity after diet shift − enzyme activity of control)/(enzyme activity after refeeding − enzyme activity of control) × 100) of the increased enzyme activities observed in refed lean Zucker rats is due simply to shifting from commercial nonpurified diet to a refined carbohydrate diet such as sucrose or starch, whereas in obese females shifting diets accounts for only 33–55% of the refeed response. Using this equation, a greater overshoot response was calculated for obese females than for their lean counterparts. The 30–50% overshoot response noted in lean female Zuckers is comparable to that observed in female Sprague–Dawley rats, whereas the 50–60% overshoot observed in obese females is close to the response (55%) noted in male Sprague–Dawleys (8).

Plasma testosterone levels in obese female Zucker rats, although substantially lower than those observed in male rats, were elevated 30% when compared to levels in the lean females. This results in a higher testosterone-to-estrogen ratio in obese as compared to lean rats. While this does not explain the obese females' elevated basal levels of hepatic lipogenic enzyme activity, nor can it account for the increased levels of these enzymes in obese Zucker males, it may contribute to the enhanced refeeding response of obese females. The impact of altered sex hormone ratios and genetic obesity on hepatic lipogenic enzymes bears further investigation.

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