Effect of Long-Term Somatotropin Treatment on Body Composition and Life Span in Aging Obese Zucker Rats

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The objective of this work was to test the hypothesis that a somatotropin (STH)-induced reduction in body fat would prolong the life span of the obese Zucker rat. Two experiments were conducted. In the first experiment, male and female, lean and obese Zucker rats were treated with STH (0 or 2 mg/d bovine STH) for 4 weeks, beginning at 7 months of age. Across phenotypes, STH treatment increased the growth rate by 159%, muscle weights by 14%, and circulating insulin-like growth factor (IGF)-1 by 23%, and decreased carcass fat by 21% ($P < 0.05$). The second experiment was a longevity trial to determine whether these changes in body composition would increase the life span of the obese rat. Beginning at 7 months of age, individually housed, male and female, lean and obese rats were assigned to daily STH treatments (0 or 2 mg/d). Rats were monitored daily, and sick or moribund rats were euthanized and necropsied to determine existing pathologies. The average life span of the lean rats was 661 days and was unaffected by STH treatment (639 days, NS) or gender. Average life span of the vehicle-injected obese rats (435 days) was less than that of the lean group ($P < 0.001$). STH treatment of the obese rats resulted in a further reduction of life span (349 days, $P < 0.02$). The predominant pathology observed across the treatment groups was renal disease, characterized by progressive glomerulonephropathy. Thus, although exogenous STH was able to reduce carcass lipid and to increase lean tissue mass in obese rats, there was no improvement in longevity. In contrast to the hypothesis, STH actually reduced the life span of the obese rat. It is likely that STH treatment accelerated the development of progressive glomerulonephropathy in the obese rat. Exp Biol Med 231:76–83, 2006

Key words: growth hormone; longevity; obesity; animal models

Introduction

Excess body fat is a health risk in the human population, and the increased mortality and morbidity associated with obesity is well documented (1, 2). Most recently, it has been suggested that life expectancy will begin to decline in the United States because of the increasing prevalence of obesity in adult humans (3).

Although a decrease in growth hormone, or somatotropin (STH), may not be the primary cause of obesity, a decrease in circulating growth hormone or in the responsiveness to simulators of STH secretion is common to obesity of various etiologies, both in humans (4) and in animal models, such as the genetically obese pig (5, 6) and the obese Zucker rat (7). Studies in humans (8), pigs (9), and rodents (10, 11) have shown that treatment with exogenous STH increases lean tissue and decreases fat mass. In addition to the association of obesity and the STH axis, there is an inverse relationship between aging and circulating growth hormone (12, 13). Studies in growth hormone–deficient adults (14) or elderly adults treated with STH report increased lean-tissue mass and bone mineralization and decreased body fat (8).

Endogenous STH secretion and circulating levels are reduced in the genetically obese Zucker rat (7). The ability of exogenous STH to decrease body fat in young, growing, obese Zucker rats has previously been shown (15, 16). The main objective of the present work was to explore the effects of STH in aging, obese rats, as compared with their lean cohorts.

Zucker and Zucker (17) first reported that the obese Zucker rat had a reduced life span relative to its lean littermate. They also reported that caloric restriction prolonged life span. The reduced life span, as well as changes in the STH axis, implied that the obese Zucker rat could be a good model in which to study the potential long-term benefits of STH treatment as a means to treat obesity and increase life span. We hypothesized that if the shortened life span of the obese rat was caused by excess body fat, treatment with exogenous STH would reduce body fat and

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lead to an increased life span. This hypothesis is supported by the finding that STH treatment increases the life span of aging mice (18).

Materials and Methods

Animals and Diets. These studies were reviewed and approved by the University of Georgia Institutional Animal Care and Use Committee. Lean and obese Zucker rats from the University of Georgia colony were used in these studies. The rats were from a closed, pathogen-free colony that was serologically monitored and free of mycoplasma, pathogenic bacteria, and murine viruses. Rats were individually housed in hanging wire mesh cages maintained at 22 ± 2°C with a 12:12-hr light:dark cycle (lights on from 0700 to 1900 hrs). The rats were given unlimited access to water and a pelleted nonpurified diet (Rodent Chow 5001; Purina, St. Louis, MO) before and throughout the experiment.

Experiment 1: Effect of Exogenous STH on Body Composition. The objective of the first experiment was to document that growth hormone treatment of 7-month-old, *ad libitum*-fed Zucker rats would reduce body fat. The procedures used were based on previous work (11, 15, 16, 19). At 7 months of age, male and female, lean and obese rats were assigned to either saline- or STH-treatment groups. There were five females and four males in each of the gender and treatment groups. In addition, three rats of each gender and phenotype were euthanized by CO_2 asphyxiation at the beginning of the experiment to establish the initial body composition. The average weight of these rats was similar to the initial weight of the rats treated with STH. Treatment group assignment was made such that the initial weight was similar for saline- and STH-treated obese rats. Rats were treated with sterile saline or bovine STH (2 mg/d; provided by Monsanto, St. Louis, MO) for 4 weeks. Somatotropin was solubilized in 25 m*M* $NaHCO_3$ (pH 9.5) at a concentration of 10 mg/ml, aliquoted into vials, and stored frozen until the time of use. Rats were injected between 1000 and 1200 hrs each day. Feed intake and body weight were monitored three times per week. The rats were euthanized by decapitation after induction of narcosis by carbon dioxide inhalation in room air. Immediately after euthanasia, trunk blood samples were obtained and allowed to clot. Serum was obtained by centrifugation (1200 *g* for 15 mins) and stored at −20°C. Liver, heart, kidney, gastrocnemius and soleus muscles, and retroperitoneal fat pads were removed and weighed. Tail length was determined, and the tibia/fibula and femur from one leg was removed for later determination of weights and lengths. The remaining, eviscerated carcass, with skin and fur attached, was used for gravimetric determination of carcass lipid (15). Serum samples were analyzed for insulin-like growth factor (IGF)-1 (16) and insulin (ICN Pharmaceuticals, Costa Mesa, CA). Bones were freed of attached tissue and dried at 100°C for 16 hrs before weighing.

Experiment 2: Effect of Exogenous STH on Longevity. The second experiment was performed to test the hypothesis that the decreasing body fat in the obese rat resulting from the STH administration would increase longevity. The study was initiated with male and female, lean and obese rats. At approximately 3 months of age, the rats were placed in individual cages, and body weight was monitored at weekly intervals (data not shown). Three of the obese female rats died before the initiation of STH treatment. At approximately 7 months of age (mean age, 208 days), lean (female, $n = 32$; male, $n = 6$) and obese (female, $n = 28$; male, $n = 8$) rats were assigned to either saline- or STH-treatment groups. Treatment group assignments were made such that the initial weights were similar for saline- and STH-treated rats in each gender and phenotype group. Rats received 0 (saline) or 2 mg bovine STH per day by subcutaneous injection. STH was prepared as described for Experiment 1. Feed intake was monitored for 5 weeks during the first part of the study (Days 16–51). During this time, rats were fed ground pellets in feed jars designed to minimize spillage. Pelleted feed was offered for the remainder of the study. Body weights were monitored three times per week, and rats were observed daily for activity and feed consumption. Rats losing greater than 20% of their weight on consecutive weighing periods were euthanized by inhalation of carbon dioxide in room air. Rats that were euthanized or died spontaneously were submitted to the Diagnostic Laboratory at the University of Georgia College of Veterinary Medicine. Tissues from all obese rats and the first 15 lean rats were examined histologically. Tissues were fixed in 10% neutral buffered formalin, imbedded in paraffin, sectioned at 4–5 μm, stained with hematoxylin and eosin, and examined with a standard light microscope. All remaining rats were euthanized at approximately 2 years of age (Day 739). Thus, the duration of STH treatment was 530 days, approximately 18 months.

Statistical Analysis. The results of Experiment 1 were analyzed as a $2 \times 2 \times 2$ design with main effects of treatment (saline or STH), gender (male and female), and phenotype (lean or obese), and their interactions included in the model. All results are reported as least-square-means and a pooled standard error. All comparisons between and among means were made with the general linear models procedure (*Proc GLM*) of SAS (Version 8.2; SAS Institute, Cary, NC). Differences were considered significant at $P < 0.05$. In Experiment 2, body weight and intake comparisons were made using the *Proc Mixed* procedure in SAS, using a repeated measures over time analysis, with rat as the random variable. Because of differences in the number of rats in each gender, results for body weight and intake are reported separately. Differences in life span were analyzed using the *Lifetest* procedure in SAS, using separate two-way comparisons of the effects of STH treatment within each phenotype and between phenotypes for the saline-treated rats. Data for rats surviving at the end of the study (Day 739) were

considered censored. Both log-rank and Wilcoxon rank sum tests are reported.

Results

Experiment 1. There were significant gender differences between male and female rats that were caused by the higher body weight and food intake in males. There were a few interactions between gender and STH and one three-way (gender × STH × phenotype) interaction for growth rate. Thus, results are shown for males and females combined. STH treatment for 4 weeks, beginning at 7 months of age, resulted in an increase in growth rate (Table 1), with a greater increase in lean (182%, $P < 0.01$) than obese rats (83%, $P < 0.05$). There was an interaction between gender and STH on body-weight gain, with males having less of a stimulation from STH than females. The three-way interaction was accounted for by the lack of any stimulation of gain in male, obese rats treated with STH. Obese rats had greater average daily feed intake than lean rats ($P < 0.001$), and male rats had a greater intake than females ($P < 0.001$). Feed intake was not affected by STH treatment ($P < 0.14$).

In the baseline group of rats, percentage of body fat was 13.7% in lean and 39.7% in obese rats (SEM = 3.0; $P < 0.001$). The percentage of body fat in control lean and obese rats at the end of the 4-weeks study was 15.5% and 43.9%, respectively, and, thus, was similar to the difference observed at the initiation of treatment. Treatment with STH resulted in a reduction in percent lipid in the carcass in both lean and obese phenotypes ($P < 0.05$). The absolute carcass lipid was reduced in lean rats ($P < 0.01$), but because of the high variation, the numerical reduction in obese rats was not significant ($P > 0.20$).

Liver, kidney, heart, and fat pad weights were greater in obese rats than in lean rats, whereas gastrocnemius weights and femur length was greater in lean rats (Table 2). Liver weights, gastrocnemius and soleus muscle weights, and femur and tibia weights were increased, and retroperitoneal fat-pad weights were reduced in lean and obese rats after STH treatment. There was an interaction between gender and STH administration ($P < 0.01$) for liver weight, which was accounted for by the greater response to STH in female rats. Tails tended to be longer in lean rats ($P < 0.10$), and tail length was increased with STH treatment ($P < 0.05$). There was no effect ($P > 0.10$) of STH treatment on bone length.

Obese rats had greater circulating levels of insulin and IGF-1 as compared with lean rats. This is similar to previous observations in younger females (16). STH treatment resulted in an increase in IGF-1 across genders. Obese rats in both genders were hyperinsulinemic and treatment with STH exacerbated the hyperinsulinemia.

Experiment 2. A total of 74 rats (38 lean and 36 obese rats) started the study. By Day 100 of treatment (308 days of age), 64 rats remained in the study, which included all 38 lean rats and 26 of the obese rats. By Day 200 of treatment, 55 rats remained in the study, which included the 38 lean rats and 17 obese rats. Body weights of the rats in the survival study through Day 200 of treatment, or 408 days of age, are shown in Figure 1. There was an interaction between phenotype and treatment ($P < 0.05$), which was accounted for by an increase in body weight of lean rats treated with STH relative to the saline-treated controls, but no increase in body weight in the obese group. Treatment with STH did not affect body weight in the obese rats at Days 50 or 100 of treatment, but, by Day 150 and 200 of treatment, there was a decrease in body weight of STH-treated obese rats. This coincided with mortality of obese STH-treated rats (Table 3). Of the 14 female obese rats in the saline-treated group, 11 survived to Day 200 of treatment. In the growth hormone–treated obese group, only 3 of the initial 14 female obese rats survived to Day 200. In the male rats, three of the four saline-treated obese rats survived to Day 200 of treatment, and none of the STH-treated male rats remained.

Feed intake was monitored from Days 16–51 of the study. As expected, obese rats had a greater food intake than lean rats (27.95 vs. 21.60 g/d; SEM = 0.69; $P < 0.001$). Males consumed more than females (27.50 vs. 22.05 g/d; SEM = 0.63 g; $P < 0.001$). The main effect of STH was to increase food intake (STH, 28.5 g/d vs. saline, 26.1 g/d; $P <$

Table 1. Effect of STH on Body Weight, Feed Intake, and Carcass Composition (Experiment 1)[a]

	Genotype								
	Lean		Obese			*P* values			
STH (mg/d)	0	2	0	2	SEM	Genotype	STH	Gender	Genotype × STH
Initial body weight (g)	420.0	420.7	732.7	731.0	17.8	0.001	0.95	0.001	0.94
Final body weight (g)	443.4	487.4	744.6	760.3	18.3	0.001	0.17	0.001	0.34
Daily gain (g/d)	0.84	2.37	0.42	0.77	0.26	0.001	0.001	0.10	0.03
Feed intake (g/d)	20.6	20.8	27.4	24.4	1.0	0.001	0.14	0.001	0.11
Carcass weight (g)	313.0	354.3	642.7	585.6	17.9	0.001	0.69	0.001	0.02
Carcass lipid (g)	48.6	33.0	262.7	213.1	20.5	0.001	0.12	0.01	0.41
Carcass lipid (%)	15.5	9.0	43.9	36.8	3.0	0.001	0.05	0.61	0.96

[a] Results represent least squares means for groups of five female rats and four male rats in each treatment. Rats were treated with 0 or 2 mg of STH for 4 weeks, beginning at 7 months of age.

Table 2. Effect of STH on Selected Tissue Weights and Endocrine Factors in Lean and Obese Rats (Experiment 1)[a]

	Genotype					*P* values			
	Lean		Obese						
STH (mg/d)	0	2	0	2	SEM	Genotype	STH	Gender	Genotype × STH
Liver weight (g)	13.9	14.1	27.5	34.6	0.9	0.001	0.001	0.001	0.001
Kidney weight (g)	2.87	2.89	5.01	5.27	0.17	0.001	0.44	0.001	0.49
Heart weight (g)	1.33	1.61	1.89	2.47	0.32	0.03	0.19	0.41	0.66
Fat pad weight (g)	3.23	2.22	9.84	6.34	0.98	0.001	0.02	0.001	0.19
Gastrocnemius (g)	2.33	2.74	2.12	2.35	0.09	0.002	0.001	0.001	0.35
Soleus (mg)	157	192	160	187	15	0.93	0.05	0.001	0.81
Tail length (cm)	17.9	18.4	17.5	18.0	0.2	0.10	0.05	0.001	0.95
Femur weight (mg)	620	674	650	694	19	0.22	0.02	0.001	0.80
Length (cm)	3.68	3.65	3.36	3.39	0.09	0.01	0.97	0.001	0.76
Tibia weight (mg)	546	600	573	607	18	0.37	0.05	0.001	0.28
Length (cm)	4.04	4.08	4.02	4.09	0.06	0.77	0.14	0.001	0.52
Insulin (U/ml)	104	158	577	774	57	0.001	0.05	0.34	0.22
IGF-1 (ng/ml)	312	517	438	578	40	0.05	0.001	0.11	0.43

[a] Results are least squares means for five female and four male rats per treatment group. Beginning at 7 month of age, lean and obese Zucker rats were treated with STH (0 or 2 mg/d) for 4 weeks.

0.02), and there was no interaction between STH and phenotype ($P > 0.20$).

Two spontaneous mortalities were observed in the obese rats before the initiation of growth hormone treatment; these rats were not included in the analysis. The first mortality during the treatment period was an obese, saline-treated female. The mortality occurred on the seventh day of the study. Of the 36 rats (28 females and 8 males) in the study, 13 died spontaneously, and 23 were euthanized because of observed morbidity (loss of body weight, unthrifty appearance, lethargy). None of the obese rats survived beyond 360 days of treatment (568 days of age). The first lean-rat mortality was a saline-treated female that died on the 211th day of treatment. Of the 38 lean rats (32 females and 6 males) that started the study, 3 died spontaneously and 35 were euthanized. The study was terminated on Day 530 of treatment (average of 739 days of age). At this time, the remaining 15 lean rats (12 female, 3 male; 10 saline-treated rats and 5 STH-treated rats) were euthanized. Despite this apparent bias toward improved survival in the saline-treatment group, there was no overall effect of STH treatment on longevity in lean rats (saline 651.1 days vs. STH 644.9 days; $P > 0.20$; Fig. 2). The life span of the lean rats in this study is likely underestimated because the study was concluded before all of the rats died or became moribund. Although there were fewer males in the study than females, there was no gender difference in survival (male rats, 508.3 days vs. female rats, 525.7 days; $P > 0.20$). The life span of saline-treated obese rats was less than that of the saline-treated lean rats (437.2 days vs. 665.1 days; $P < 0.0001$). STH treatment of obese rats resulted in a further reduction in life span.

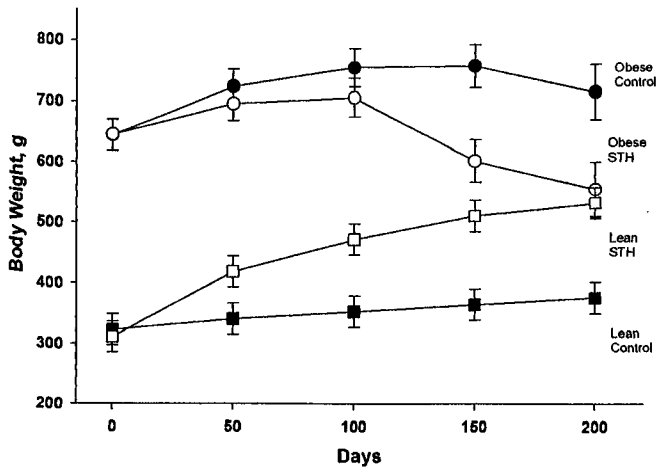

Figure 1. Effect of STH treatment on body weight in lean and obese Zucker rats. Average body weight through the first 200 days of treatment with 0 or 2 mg/d bovine STH in lean and obese rats is shown. See Table 3 for more details.

Histopathology was performed on 34 of the 36 obese rats and on 14 of the 38 lean rats. This represented animals in the first 400 days of the study. The major postmortem finding at the time of death was end-stage glomerulonephropathy (Table 5). Based on this summary, there was no apparent difference in renal pathology caused by STH treatment in lean or obese Zucker rats.

Discussion

Interest in the use of STH as an anti-aging or anti-obesity treatment increased as recombinant STH became available (8, 12–14). Our interest was in determining whether the obese Zucker rat would be useful as an animal model for investigation of the mechanisms involved in this potential application. The rats used in these experiments had established obesity and, thus, would be representative of an obese adult. Our hypothesis was to determine whether STH

Table 3. Characteristics of the Animals in Experiment 2[a]

		Genotype					*P* values		
		Lean		Obese					
STH (mg/d)		0	2	0	2	SEM	Genotype	STH	Genotype × STH
Female body weights	Initial	286.7 (16)	274.8 (16)	583.3 (14)	588.9 (14)	13.5	0.001	0.81	0.51
	Day 50	300.8 (16)	385.1 (16)	653.4 (11)	658.7 (12)	14.5	0.001	0.005	0.001
	Day 100	311.7 (16)	438.8 (16)	682.8 (11)	705.3 (8)	15.6	0.001	0.001	0.002
	Day 150	321.9 (16)	474.3 (16)	702.0 (11)	609.0 (7)	18.9	0.001	0.08	0.001
	Day 200	332.0 (16)	494.7 (16)	661.6 (11)	555.3 (3)	19.2	0.001	0.21	0.001
Male body weights	Initial	516.0 (3)	506.7 (3)	855.7 (4)	844.2 (4)	24.9	0.001	0.68	0.97
	Day 50	556.3 (3)	598.0 (3)	916.5 (4)	846.0 (3)	34.4	0.001	0.67	0.13
	Day 100	577.0 (3)	652.3 (3)	953.5 (4)	707.3 (3)	61.4	0.001	0.18	0.02
	Day 150	599.0 (3)	715.0 (3)	917.8 (4)	558.0 (1)	63.3	0.32	0.15	0.01
	Day 200	609.7 (3)	734.0 (3)	917.3 (3)	— (0)	39.5	0.002	0.07	—

[a] Results are least squares means for groups of lean and obese rats treated with saline or STH beginning at 7 months of age. Numbers in parentheses are the number of animals surviving on that day of treatment.

treatment of the obese Zucker would result in a loss of body fat and whether this loss of body fat would contribute to longevity.

Our previous research with STH treatment of has been in pituitary-intact female rats (11, 16). Most of the animals available for study in these experiments were also female, with a limited number of male rats. Treatment of aged obese Zucker rats with STH resulted in an approximate 20% decrease in body fat. Growth rate and muscle and bone weights were increased, all similar to previous work and supportive of an increase in lean-tissue mass. This extends previous observations in both *ad libitum*-fed and food-restricted younger rats (11, 15, 16). There were gender differences in the response to STH that are consistent with previous observations in the literature. In part, these are explained by the lower number of male rats in the study and the greater variability in body weight, but are also likely

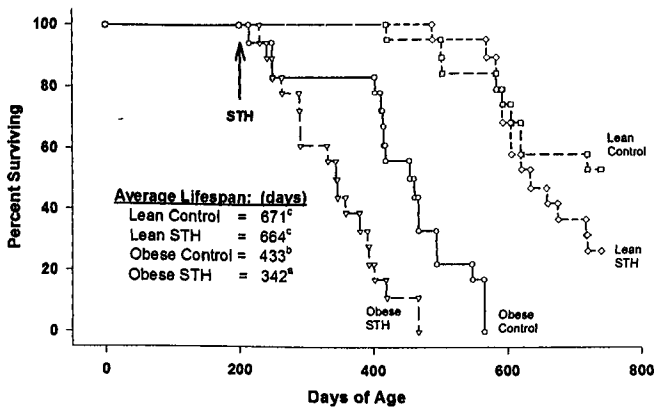

Figure 2. Survivorship of lean and obese Zucker rats treated with STH. There were 18 obese (14 female and 4 male) rats in each of the control and STH-treatment groups and 19 lean (16 female and 3 male) rats in each group. There were no significant differences between genders (see Table 4). Comparison of average life span based on mean separation using the *LS means* procedure in *Proc GLM* of SAS. Two-way comparisons of selected groups are shown in Table 4. Arrow indicates the initiation of STH treatment.

accounted for by differences in the STH status (20). The effects of STH on insulin and IGF-1 and the differences between the responses in each phenotype or gender are consistent with the literature (16, 21).

Contrary to the hypothesis that a reduction in body fat induced by STH treatment would result in an increase in life span, obese rats treated with STH had a further reduction in longevity. The differences in life span of the saline-treated lean and obese rats are consistent with other reports in the literature (22). The lack of effect of STH on the life span of lean rats is in agreement with a study reported with F344 rats (23). The further reduction in life span of STH-treated obese rats, although in opposition to our hypothesis, is consistent with other reports in the literature regarding the effects of STH in rodents and the expected effects on the kidney (24). Circulating levels of growth hormone have been correlated with the severity of renal pathology in aging rats (25). Reduced life span is a consistent finding in mice overexpressing STH (26, 27). Life-span extension is reported in dwarf mice that are growth-hormone deficient (28, 29). It has been reported that growth-hormone treatment helped ameliorate the condition of nephrectomized, uremic rats (30), but this may be accounted for by effects on protein accretion rather than by direct effects on the kidney.

As in other animal models, feed restriction of the obese rat can increase life span (22, 31) and improve renal status (32, 33), but does not reduce body-fat percentage. Zucker and Zucker (17) reported a 78% mortality in *ad libitum*-fed obese rats in the first year of life. This was reduced to an 11% mortality with feed restriction. Details of the experimental procedures, such as the level of restriction, time of implementation, or the effects on body composition and growth rate were not reported. Based on other restriction studies in the Zucker rats (34–37), it is likely that this improvement in longevity occurred without a change in body-fat percentage. Thus, the effects of caloric restriction on longevity are likely independent of adiposity

Table 4. Summary of Two-Way Comparisons of Life Span[a]

Main effects	Comparison	Average life span (days)	Test, *P* value	
			Log-rank	Wilcoxon rank sum
Phenotype (saline-treated only)	Lean (19)	651.1 ± 22.4	—	—
	Obese (18)	437.2 ± 25.2	0.0001	0.0001
Gender	Male (14)	508.3 ± 46.3	—	—
	Female (60)	525.7 ± 20.3	0.81	0.61
	Lean, control (19)	651.2 ± 22.4	—	—
	Lean, STH (19)	644.9 ± 16.1	0.18	0.34
	Obese, control (18)	437.2 ± 25.2	—	—
STH	Obese, STH (18)	342.8 ± 17.4	0.001	0.005

[a] Results represent summary of 19 saline-treated and 19 STH-treated lean rats and 18 saline-treated and 18 STH-treated obese rats. Survival times for lean rats are underestimated because the study was ended before all rats had died or had become moribund. Data for these rats was censored in the statistical analysis. Numbers in parentheses are the number of animals on which the analysis is based.

(38). The advantage conferred by STH that was of interest in the present study was a reduction in fat. Testing this hypothesis in the Zucker rat has the potential to validate this model for the study of the effects of STH as both an anti-obesity and anti-aging factor, both of which would be of interest for human health. However, based on the results of this work, it would seem that the obese Zucker rat is not a good model for study of the interaction of the effects of STH on obesity and aging in humans. It is likely that the negative effect of STH on life span in the obese rats is related to the enhancement of hereditary progressive nephropathy (25, 27–29) in obese Zucker rats.

In young, growing lean rats, STH treatment results in a stimulation of feed intake (11, 19). This is accounted for by STH stimulation of protein accretion and inhibition of lipid deposition, resulting in an increase in total energy retention and, thus, food intake (39). In animals with relatively greater rates of lipid deposition, such as the pig (40) and growing obese rat (15), STH treatment stimulates protein accretion, but the inhibition of lipid accretion is of a greater magnitude, and results in a reduction in total energy retained and a reduction in food intake. In Experiment 1, there was no significant effect of STH on food intake, but in Experiment 2, STH treatment resulted in a 9% increase in food intake. It is hypothesized that this increase, even in obese animals, is caused by a stimulation of protein deposition, resulting in a greater need for dietary amino acids (39). In contrast to previous work in younger, obese Zucker rats (15), the obese rats in this study had limited lipid accretion at the time of treatment. This statement is supported by the lack of change in body fat noted between the baseline and treated rats in Experiment 1.

Table 5. Summary of Primary Postmortem Findings (Experiment 2)[a]

	Lean		Obese	
STH (mg/d)	0	2	0	2
No. rats examined	5/19	9/19	18/18	16/18
Glomerulonephropathy (stage)				
4	2	3	16	11
3	0	2	2	2
2	2	3	0	1
1	0	1	0	2
Mammary fibroadenoma	1	—	—	—

[a] Animals that died or were euthanized during the first 400 days of the study were submitted to the veterinary diagnostic lab for necropsy, and histologic examination was conducted. The primary postmortem observations are listed. Glomerulonephropathy was scored on a four-point scale, with four being the most severe.

Across genotypes and treatments, progressive glomerulonephropathy was the primary cause of mortality or morbidity in this study. This age-related condition is recognized as one of the most common causes of morbidity and mortality in susceptible strains of aging laboratory rats (41, 42). This condition has been previously described in the obese rat as a "premature glomerulosclerosis" (33). Others have suggested that the increase in circulating lipid levels in the obese rat may precipitate kidney lesions (41). The apparent exacerbation of the renal lesions is consistent with recent studies reporting a reduced life span in transgenic mice that overexpress STH (27, 43) and have an extended life span when the growth hormone/IGF-1 axis is suppressed (28). The present study suggests that, because of the potential renal effects of STH, the obese Zucker rat may not be an appropriate model for the study of life span enhancement by STH. Similar responses to STH have not been reported in humans, in fact, growth-hormone treatment of pituitary-deficient adult humans was reported to improve renal function (44).

In summary, the average life span of obese Zucker rats was approximately 214 days shorter than that of their lean littermates (437 vs. 651 days; $P < 0.001$). Treatment of old, obese rats with STH resulted in increased lean tissue and bone mass, and decreased fat mass; changes similar to those reported in elderly humans (8). Despite the reduction in body fat, life span was not improved in STH-treated obese rats. In fact, life span was significantly reduced by growth-hormone treatment in obese rats (343 vs. 437 days; $P < 0.01$) but not in lean rats (651 vs. 645 days; NS). This may

be associated with the enhancement of genetic predisposition to progressive renal disease.

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