0013-7227/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(3):1234–1240

doi: 10.1210/jc.2002-021695

Serum Leptin Levels as a Marker for a Syndrome X-Like Condition in Wild Baboons

WILLIAM A. BANKS, JEANNE ALTMANN, ROBERT M. SAPOLSKY, JANE E. PHILLIPS-CONROY, AND JOHN E. MORLEY

Geriatric Research, Education and Clinical Center, Veterans Affairs Medical Center-St. Louis (W.A.B., J.E.M.), St. Louis, Missouri 63106; Division of Geriatrics, Department of Internal Medicine (W.A.B., J.E.M.), Saint Louis University School of Medicine, St. Louis, Missouri 63104; Biology Department (R.M.S.), Stanford University, Stanford, California 94305; Department of Anthropology (J.E.P.-C.), Washington University, St. Louis, Missouri 63130; Department of Anatomy and Neurobiology (J.E.P.-C.), Washington University School of Medicine, St. Louis, Missouri 63110; Institute of Primate Research (J.A., R.M.S.), National Museums of Kenya, Nairobi, Kenya; Department of Ecology and Evolutionary Biology (J.A.), Princeton University, Princeton, New Jersey 08544; and Department of Conservation Biology (J.A.), Chicago Zoological Society, Brookfield, Illinois 60513

We measured serum leptin levels in two groupings of wild male baboons, one with access to abundant quantities of food from gardens and garbage dumps near human habitations (Garbage; n = 11) and one without access (No Garbage; n = 10). A Garbage subgroup had high leptin levels (Garbage HL), whereas the rest of the Garbage group had low leptin levels (Garbage LL) similar to those in the No Garbage group. The Garbage HL individuals were obese, with higher mass, body mass index, and leptin to mass ratios; were insulin to resistant, with elevations in serum insulin, glucose, and insulin to glucose ratios; and were hyperlipidemic. This syndrome X-like condition occurred only in the Garbage HL subset. The Garbage LL subset did not differ from the No Garbage individuals in mass, body mass index, leptin to mass ratio, insulin, glucose, or insulin to glucose ratios. The highest cholesterol levels, however, occurred in the Garbage LL individuals, suggesting that susceptibility to hyperlipidemia is distinguishable from susceptibility to obesity and insulin resistance. The differences were not explained by age or social status. These results show that a subgroup of wild baboons is susceptible to developing obesity and insulin resistance and that this susceptibility is not related to age or social rank. (*J Clin Endocrinol Metab* 88: 1234–1240, 2003)

LEPTIN, A 16-KDA PROTEIN secreted by fat cells, is a major regulator of body adiposity (1, 2). The actions of leptin depend on its ability to cross the blood-brain barrier and to act on receptors within the central nervous system where it affects feeding, thermogenesis, and activity (3–5). Humans and animals with defects in the production of leptin, in the ability of the blood-brain barrier to transport leptin, or in receptor and postreceptor function are obese and often have elevated glucose and insulin levels and fatty livers (1, 2, 5–9). In animals with little or no leptin production, exogenous administration of leptin dramatically reduces obesity, restores fertility, and reverses insulin resistance and fatty liver (4, 5, 7, 10, 11). Most obese humans have elevated levels of leptin, demonstrating a resistance to leptin (12, 13). In such cases, exogenous leptin is less effective in reducing weight (14, 15).

Why obesity and leptin resistance should be so common in a system as tightly regulated and with as many redundant systems as body weight is unclear. One view is that leptin did not evolve as a signal of excess adiposity to the brain, but rather that low levels of leptin were used to signal starvation to the brain (16). A variation on this hypothesis is that leptin evolved as a metabolic switch, indicating to the brain when adipose stores were adequate for the animal to engage in activities not related to seeking food, such as reproduction, without endangering survival. Such a hypothesis explains why an adiposity signal is also able to induce puberty, improve immunity, promote angiogenesis, increase bone density, and reverse changes associated with starvation (10, 17–20). This view predicts that leptin and its feedback loop evolved to be more efficient at lower levels of leptin than those considered as normal in Western societies.

That the ancestral level of leptin was lower and may have played a different role than that assumed at higher levels is supported by the finding that leptin levels are considerably lower in wild, healthy baboons than in captive animals (21). Such wild animals ingest the same amount or more calories than counterparts living in captivity but use most of those calories in activity. Healthy wild animals not only weigh less because of decreased adiposity, but may also have an absolute increase in muscle mass.

To better understand the shift in adiposity, the alteration in metabolic signals, and the changes in morphology when a population of foragers becomes more sedentary, we examined a natural experiment with a population of wild baboons. We compared two categories of wild baboons: one that gathered all of its food from wild conditions, and another that had an abundance of food with little energy expended in feeding from the gardens and garbage dumps near human habitation. Other than differences in food sources and availability, all individuals lived in the wild and have been the subject of intensive study for over a decade. We compared serum levels of leptin, glucose, insulin, total cho-

Abbreviations: BMI, Body mass index; HL, high leptin; IBW, ideal body weight; LL, low leptin.

lesterol, body weight, crown-rump length, age, and social status for these groups.

Materials and Methods

Collection of baboon data

Baboons (*Papio cynocephalus*) were treated humanely throughout the study and in accordance with National Institutes of Health guidelines. The 21 males in this study were members of three social groups within the baboon population of Amboseli National Park and its environs, a semi-arid grassland savannah in southern Kenya. The groups are part of long-term studies of individually identified animals for which demographic, reproductive, and behavioral data are gathered on an almost daily basis. Two of these groups (n = 10) subsisted entirely through foraging on wild food and traveled 8–10 km/d to obtain food and water (No Garbage). Their diet was mostly vegetarian, consisting of grass blades and corms, shrubs, tubers, and various parts of *Acacia* (*xanthophlea* and *tortilis*) trees. Nearby, another group (n = 11) lived near tourist lodges and spent part of each day foraging on the plants in the tended gardens there and feeding on the kitchen and dining room leavings that were deposited in the lodges' refuse dump (Garbage). Although their diet also consisted primarily of vegetable matter and had a similar fat content, the food was abundant, easy to digest, and readily accessible. The two types of groups ate a similar number of daily calories; however, the garbage-feeding group traveled about one third the daily distance in seeking food. Both sets of baboons have been extensively studied, and a number of behavioral and biological data have been previously reported from them (22–25). For individuals born into study groups, almost all birth dates are known within a few days; for adult males that immigrate into study groups from nonstudy groups, age is estimated upon immigration, independently by several observers, using operational criteria based on patterns of maturation and aging of a large set of known-age individuals. Agonistic dominance rank is calculated each month based on pairwise wins and losses (26–28). All adult and subadult males rank above all females, most agonistic interactions occur between members of the same sex, and a linear ranking among adults of each sex can readily be constructed from the pairwise outcomes. Rank among juvenile males is primarily determined by age and size (29). Rank scores reported for adults represent their social rank at the time of darting, and scores for juveniles represent their mother's rank at time of conception or birth.

Individual baboons were darted with Telezol (tiletamine hydrochloride and zolazepam) injected by a syringe delivered by a blowpipe from 10 m or less. Animals were darted between 0730 and 1030 h from July through October, during the long dry season. Most animals had already eaten some food, and so insulin and glucose values are not fasting values. Sedated baboons were weighed to the nearest 0.1 kg, and crown-rump lengths were measured. A body mass index (BMI) was calculated by dividing mass (in kilograms) by the square of the crown-rump length (in meters). Blood was drawn from the femoral vein within 15 min of darting, all samples were immediately put on ice and centrifuged, and the serum was frozen within 1 h.

Blood assays

The kit for human leptin (Linco Research, Inc., St. Charles, MO) was used to measure leptin. The kit is 100% cross-reactive with baboon leptin. As previously reported, insulin was measured by RIA with the kit from Cambridge Medical Technology (Billerica, MA), and glucose was measured by the glucose oxidase method (30). Plasma total cholesterol was measured enzymatically (31).

Statistical analysis

Means are reported with their SE values and the number per class of individuals. Paired means were compared by Student's *t* test. More than two means were compared by ANOVA, followed by Newman-Keuls range test. Statistical significance was taken to be *P* value less than 0.05. Regression lines were calculated by the least-squares method using the Prism 3.0 program (GraphPad Software, Inc., San Diego, CA) and are reported with their correlation coefficient (r), slope, intercept, number (n), and *P* value.

Results

Leptin values differed between the baboons that fed entirely on naturally occurring foods (No Garbage, 1.38 ± 0.10 ng/ml; n = 10) and those that supplemented their wild diet and spent less time foraging (Garbage, 5.40 ± 1.76 ng/ml; n = 11) as measured by a two-tailed, unpaired *t* test [$F_{(1,19)} = 2.28$; $P < 0.05$]. Because variances were not equal, results were tested with nonparametric statistics. The groups were statistically different when compared with Welch's correction and by the Mann-Whitney test. The coefficient of variation was greater than 100% for the garbage-feeding group, whereas it was only 22% for the No Garbage group. As Fig. 1 shows, the Garbage group consisted of two subgroups: those with high leptin levels (Garbage HL) and those with low leptin levels (Garbage LL). The Fig. 1 *inset* shows that the means for these three groups were 1.38 ± 0.10 ng/ml for the No Garbage group (n = 10), 1.59 ± 0.19 ng/ml for the Garbage LL group (n = 7), and 12.1 ± 2.25 ng/ml for the Garbage HL group (n = 4). ANOVA showed statistically significant differences among these groups [$F_{(2,20)} = 51.9$; $P \ll 0.01$]. The Newman-Keuls range test showed that the Garbage HL group differed from the other two groups ($P \ll 0.01$ for both comparisons), but the Garbage LL did not differ from the No Garbage group. The three groups of No Garbage, Garbage LL, and Garbage HL were compared in subsequent analyses.

Mass was greater in the Garbage HL group than in the other two groups, but the three groups did not differ in either crown-rump length (Table 1) or age. Leptin and mass were not correlated in the No Garbage or Garbage LL groups, and there was an inverse correlation in the Garbage HL group (data not shown). Age and leptin levels were inversely correlated in the Garbage LL group ($P < 0.05$) but not in the other two groups (Fig. 2, *top panel*). The ANOVA for BMI (Fig. 2, *bottom panel*) was significant [$F_{(2,20)} = 5.57$; $P < 0.05$]. The range test showed that the BMI for the Garbage HL group, which was about 50% higher than for the other two groups, was different from the BMI for the No Garbage ($P < 0.01$) and

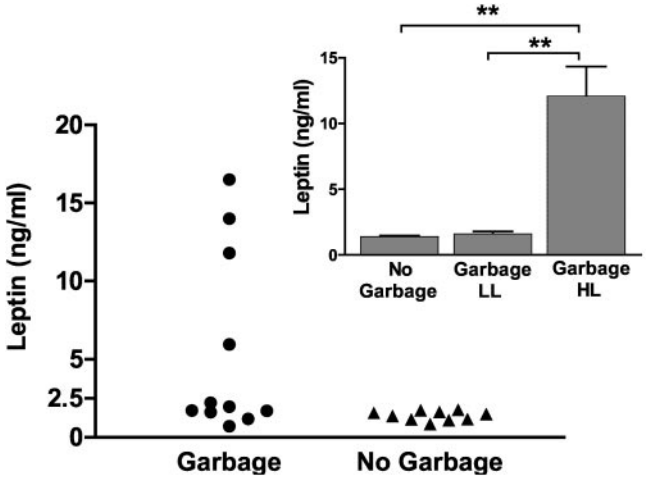

FIG. 1. Serum leptin levels in wild baboons. The *scatterplot* shows that a subgroup of the Garbage group had high leptin levels (Garbage HL) and the remainder had low leptin levels (Garbage LL). The *inset* shows the mean and SE of the three groups of baboons. **, $P < 0.01$.

TABLE 1. Body weight and crown-rump length in wild baboons

Group (n)	Mass (kg)	Crown-rump length (cm)
No Garbage (10)	18.4 ± 3.0	64.8 ± 3.5
Garbage (11)	20.2 ± 3.6	63.1 ± 3.6
LL (7)	14.6 ± 3.7	58.5 ± 4.7
HL (4)	30.0 ± 4.4	71.2 ± 3.2

Means are presented with their SE. The HL group was statistically different from the LL and No Garbage groups in mass ($P < 0.01$) but was not different in crown rump-length.

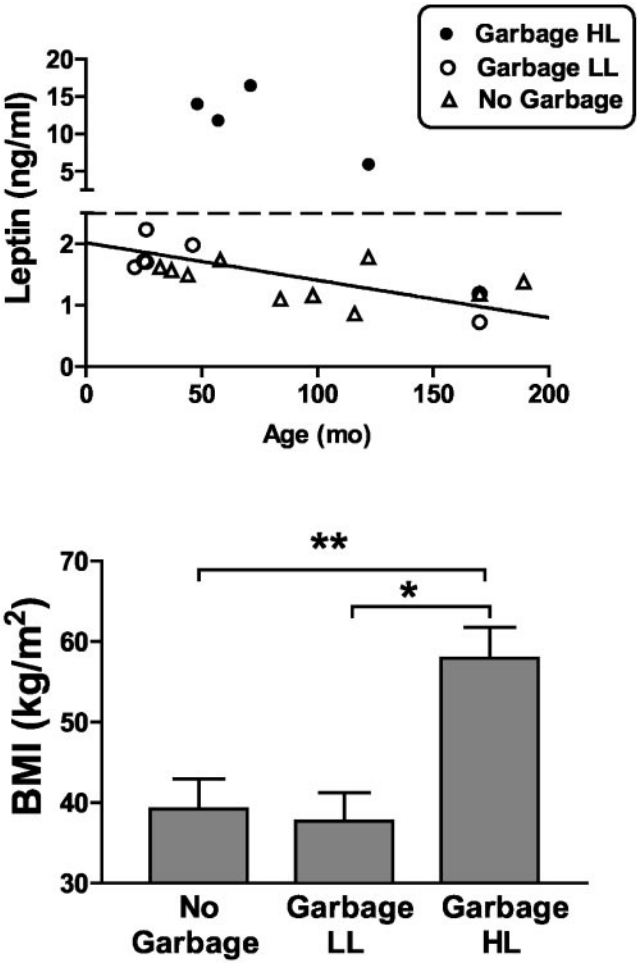

FIG. 2. Age and BMI in three groups of wild baboons. *Top*, An inverse relation between age and serum leptin levels occurred for the Garbage LL group; the age distribution for the Garbage HL group was not statistically different from the other two groups. *Bottom*, BMI was greater in the Garbage HL group, with no difference between the other two groups. *, $P < 0.05$; **, $P < 0.01$.

Garbage LL ($P < 0.05$) groups. There was no correlation between BMI and leptin levels for any group (data not shown). The leptin to mass ratio was much higher in the Garbage HL group and decreased with age (Fig. 3). The correlation between the leptin to mass ratio and age was significant for the No Garbage ($P < 0.01$; n = 10), the Garbage LL ($P < 0.01$; n = 7), and the Garbage HL ($P < 0.05$; n = 4) groups.

In human studies, weight is often expressed relative to a calculated ideal body weight (IBW). To do this for baboons, we first had to determine what an IBW would be for our

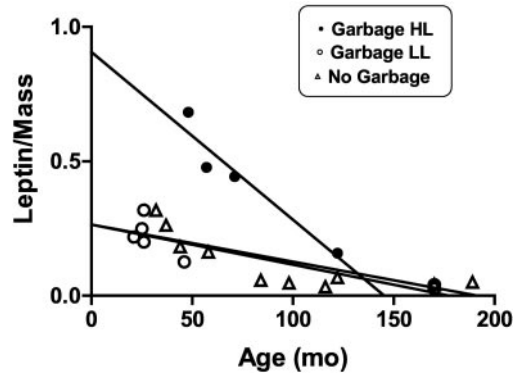

FIG. 3. Relation between age and leptin/mass ratio. The leptin/mass ratio, used as an index of obesity, was inversely related to age in all groups. This relation was greatly accentuated in the Garbage HL group.

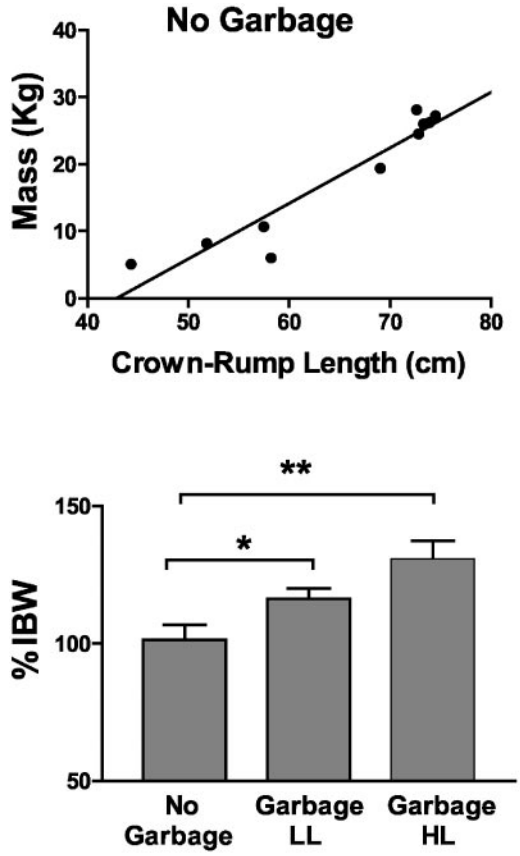

FIG. 4. IBW. *Top*, The relation between mass and crown-rump length for the No Garbage groups. The IBW for a given crown-rump length was calculated on the basis of this regression line. *Bottom*, Garbage LL and Garbage HL groups had elevations in %IBW. *, $P < 0.05$; **, $P < 0.01$.

population. We did this by regressing mass against crown-rump length for the No Garbage group. The correlation was highly significant (r = 0.949; n = 10; $P \ll 0.01$; slope = 0.829; intercept = −35.6; Fig. 4, *top panel*). We used this equation to calculate the IBW for garbage-feeding baboons on the basis of their crown-rump lengths. We found that the Garbage LL group weighed 16% over IBW and the Garbage HL group weighed 31% over IBW (Fig. 4, *bottom panel*). The ANOVA

was significant [$F_{(2,20)} = 6.54$; $P < 0.01$], and the range test showed that the body weights for both the Garbage LL ($P < 0.05$) and Garbage HL ($P < 0.01$) groups were statistically different from those of the No Garbage group.

Insulin and glucose were both greater in the Garbage HL group than in either of the other groups (Fig. 5). For insulin, means for the three groups were 18.5 ± 6.1 μU/ml (No Garbage; n = 8); 26 ± 4.5 μU/ml (Garbage LL; n = 6); and 192 ± 70.7 μU/ml (Garbage HL; n = 4). The ANOVA for insulin was $F_{(2,17)} = 11.2$ ($P < 0.01$), and the range test indicated that the Garbage HL group differed from both of the other groups at the *P* value less than 0.01 level. The Garbage LL and No Garbage groups did not differ, even when a Student's *t* test was performed on just those two groups. For glucose, the means were 73.6 ± 2.6 mg/dl (n = 8), 74.5 ± 6.5 mg/dl (n = 6), and 96.5 ± 8.0 mg/dl (n = 4) for the No Garbage, Garbage LL, and Garbage HL groups, respectively. The ANOVA showed a difference [$F_{(2,17)} = 4.91$; $P < 0.05$], and the range test showed that the Garbage HL group differed from the other two groups at the *P* value less than 0.05 level. The ANOVA for the insulin to glucose ratio showed differences [$F_{(2,17)} = 14.8$; $P < 0.1$], and the range test showed that the Garbage HL group differed from the No Garbage ($P \ll 0.01$) and Garbage LL ($P \ll 0.01$) groups. The insulin to glucose ratios for the No Garbage and Garbage LL groups did not differ, even when compared by Student's *t* test.

Cholesterol showed a different pattern than insulin, glucose, body mass, BMI, or leptin (Fig. 5, *bottom right panel*). Both the Garbage LL (n = 5; $P < 0.01$) and the Garbage HL (n = 4; $P < 0.05$) groups were statistically different from the No Garbage group (n = 6) but not from each other [$F_{(2,14)} = 11.58$; $P < 0.01$]. One No Garbage animal was a statistical outlier with a value of 191 and was excluded from analysis.

To further characterize the Garbage group, we determined which animals had abnormal chemistries. In construction of medical tests, abnormal values are defined as those which are greater than 2–3 SD values above the mean. We first determined the mean and SD for the No Garbage animals and then determined which animals had chemistry values greater than 3 SD values above the mean values. None of the No Garbage animals had abnormal values by this criterion. The results for the Garbage LL and Garbage HL animals are shown in Table 2. Garbage HL animals also accounted for the animals with abnormal insulin levels, for two of the three animals with hyperglycemia, and for four of the five animals with elevated insulin to glucose ratios. In contrast, none of the Garbage HL animals had abnormal cholesterol levels,

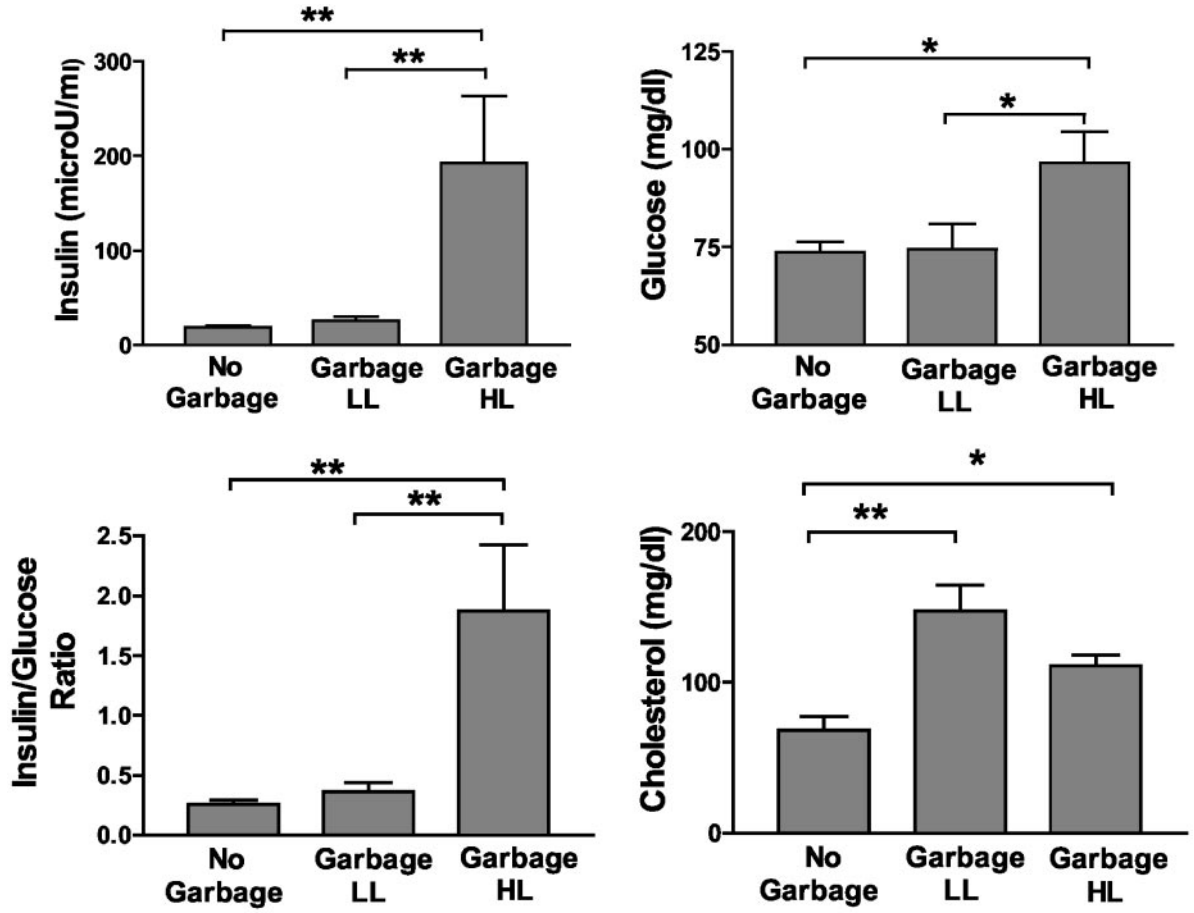

FIG. 5. Metabolic parameters. *Top left*, Serum insulin levels were greatly elevated in the Garbage HL group but not the Garbage LL group. *Top right*, Glucose levels were elevated in the Garbage HL group but not in the Garbage LL group. *Bottom left*, The insulin/glucose ratio was elevated in the Garbage HL group but not the Garbage LL group. *Bottom right*, Cholesterol was elevated in the Garbage LL group and the Garbage HL group. *, $P < 0.05$; **, $P < 0.01$.

TABLE 2. Serum chemistry values in garbage-feeding baboons

Animal group	Leptin (ng/ml) *1.38 ± 0.30*	Insulin (μU/ml) *18.5 ± 6.1*	Glucose (mg/dl) *73 ± 7.3*	Insulin/glucose ratio *0.256 ± 0.097*	Cholesterol (mg/dl) *68 ± 22.3*	Diagnosis
LL	0.72	33	**101**	0.33	**145**	Diabetes and hyperlipidemia
LL	1.17	27	63	0.43	**201**	Hyperlipidemia
LL	1.19	10	75	0.13	100	
LL	1.62	NA	NA	NA	NA	
LL	1.72	31	54	**0.57**	NA	Insulin resistance
LL	1.98	16	79	0.20	127	
LL	2.23	**39**	75	0.52	**165**	Insulin resistance and hyperlipidemia
HL	**5.96**	**125**	**99**	1.26	108	Diabetes and insulin resistance
HL	**11.8**	**63**	79	**0.80**	98	Insulin resistance
HL	**14**	**389**	**117**	**3.32**	132	Diabetes and insulin resistance
HL	**16.5**	**193**	91	**2.12**	106	Insulin resistance

The mean ± SD for each chemistry, as derived from the No Garbage group, is shown in each column header in *italics*. Abnormal values (defined as ± 3 SD from mean) are given in *bold*. No abnormal values occurred in the No Garbage group. NA, Not available. Abnormal values for leptin, insulin, glucose, and the insulin to glucose ratio clustered in the HL group, whereas abnormal cholesterol levels were found in the LL group.

whereas three of five Garbage LL animals had elevated cholesterol levels.

Leptin status and rank were not clearly related among the Garbage baboons. Among the three Garbage adults, two were LL; one Garbage LL was very high (2/9) and the other was lowest (9/9) in social rank. Of the three Garbage subadults, all were HL. Two were brothers, and all three were offspring of the two fattest adult females in the group; the mothers were of mid-to-low social rank. All of the Garbage juveniles were LL. At the time of their conception, their mothers ranged from a high (2/12) to a low (11/11) social rank.

Discussion

This study took advantage of a unique, natural experiment in which animals living in the wild and exposed to an abundant, readily available source of food primarily in the form of discarded kitchen and table scraps (Garbage group) could be compared with other wild animals without access to garbage (No Garbage group). We compared morphological, metabolic, and social parameters. The baboons with access to garbage, not surprisingly, had a higher BMI and higher serum leptin levels than the No Garbage group. We confirmed our earlier findings that healthy wild baboons have serum leptin levels much lower than those considered normal for Western humans and animals living in captivity (21). Several other major findings, however, were not predicted. First, only a subgroup of baboons with access to garbage had elevated levels of serum leptin and were grossly overweight (Garbage HL). This subgroup was not the youngest or oldest, nor was it distinguished by social rank. Second, obesity and insulin resistance, previously reported in the group with access to garbage (24, 30) clearly segregated to the baboons with elevated leptin levels. Members of the Garbage HL group also had elevated cholesterol levels, so that they had a syndrome X-like condition. Third, the subgroup of wild baboons that did not have elevated leptin levels despite access to garbage (Garbage LL) did not develop insulin resistance, hyperinsulinemia, or hyperglycemia but did contain the individuals with the highest cholesterol levels. Therefore, obesity and hyperlipidemia were overlapping but independent susceptibilities in this population of baboons.

The Garbage and No Garbage groups ingested about the same number of calories per day, and the diet had a similar fat content (32). The No Garbage group spent considerably more time and effort every day in obtaining and extracting foods. The Garbage group had abundant food available throughout the year at a refuse dump, traveled about one third the distance, and spent less than half the time feeding in comparison to the No Garbage group (23, 24, 32). Not surprisingly, the Garbage and No Garbage groups differed in their leptin levels. However, unequal variances and a large coefficient of variation for the Garbage group indicated that there might be subgroups. Figure 1 shows that this was indeed the case.

Of the 11 baboons who had access to garbage, four (Garbage HL) had serum leptin levels that were more than 3 SD above the mean of the No Garbage group. The mean leptin level for the Garbage HL group was more than seven times greater than the means for either the Garbage LL or the No Garbage group. The Garbage HL group also had BMI values that were greater than those of either the Garbage LL or No Garbage groups. In comparison, the Garbage LL group did not differ from the No Garbage group in serum leptin levels, mass, or BMI, even when compared by *t* test. All animals with access to garbage ate from it regularly, and the Garbage LL group was not observed partaking of garbage less than the HL group. Therefore, the HL subgroup represents a difference in susceptibility to obesity.

Leptin also seems to decrease with age in these male baboons, a relation which was statistically significant for the Garbage LL group (Fig. 2, *top left panel*). In our previous study, we found a similar relation for baboons living in the wild in Ethiopia and in captivity (21). This is also consistent with previous findings showing that captive baboons become more lean as they age (33, 34). To further assess the relations among mass, age, and adiposity, we compared the leptin/mass ratios and percent of IBW(%IBW) among the three groups.

Because mass increases with age, the leptin/mass ratio and %IBW will partially correct for age differences. It also indicates the relative amount of body mass that is fat as measured by leptin. The leptin to mass ratio showed the following: 1) the Garbage HL group is much more obese at any given age than the other two groups; 2) the Garbage LL and No Garbage groups do not differ in the relation between

body fat and age; and 3) all three groups become increasingly lean with age.

Norms for the relation between mass and height, or IBW, are well established in humans. Here, we used the strong linear relation between crown-rump length and mass in the No Garbage group to construct such a relation for baboons. We found the Garbage LL group was about 15% over IBW, and the Garbage HL group was about 30% over. The IBW analysis, therefore, shows that whereas most baboons are susceptible to increased weight gain when exposed to ready calories, there is a subset that is more susceptible to laying down these calories as fat.

Unlike in humans, leptin did not correlate strongly with mass, BMI, or %IBW. This lack of correlation may be explained by the hypothesis that leptin at low levels is not so much a signal to the brain that an individual is becoming obese as it is a signal that adequate nutritional reserves exist for activities other than seeking food, such as reproduction (35). It should be noted that even the highest leptin level in the Garbage HL group (16.5 ng/ml) would not be indicative of obesity in a human population (12, 13). The mean leptin level of 12.1 ng/ml for the Garbage HL group is near that reported for humans. Similarly, the body fat composition of female garbage-feeding baboons has been measured to be about 23%, a value similar to that of Western human females (24).

The metabolic profile of the Garbage HL group showed them to have insulin resistance, whereas the No Garbage and Garbage LL groups did not. Insulin resistance was evidenced by the elevations in insulin and the insulin to glucose ratio. Serum glucose was also higher than in the Garbage HL group, but the mean value of 96.5 ± 16 mg/dl would still be well within the normal limits seen in human populations. Cholesterol levels, in contrast to glucose and insulin, were elevated in both groups with access to garbage (Fig. 5, *bottom right panel*). The combination of elevated glucose, insulin, and lipids with obesity strongly suggests that the garbage HL baboons were developing a condition similar to syndrome X. As in human populations, this syndrome was developing in only a susceptible subset of those exposed to excess calories.

To further determine the relevance of elevations in the serum chemistries, we considered a value more than 3 SD above the mean of the No Garbage group as abnormal (Table 1). By this criterion, none of the No Garbage baboons had any abnormal chemistries. Abnormal insulin levels and insulin to glucose ratios segregated to the Garbage HL group, whereas all of the elevated cholesterols were in the Garbage LL group. None of the baboons with abnormal insulin levels or insulin to glucose ratios had abnormal cholesterol levels. This suggests that although obesity, hyperlipidemia, hyperglycemia, and hyperinsulinemia were all associated with the exposure to excess calories and the more sedentary lifestyle of the Garbage groups, the susceptibility to hyperlipidemia segregated to a group different from that of insulin resistance and obesity. Using the criterion of a value 3 SD above normal to make medical diagnoses, we found that all of the Garbage HL group had insulin resistance (defined as an elevated insulin or insulin to glucose ratio), and two had diabetes mellitus. Four of the Garbage LL baboons had diabetes mellitus, hyperlipidemia, or insulin resistance.

Insulin resistance, hyperglycemia, fatty liver, and obesity are not caused by leptin but by an ineffective response to leptin within the brain. Humans with lipodystrophy have little or no fat and, therefore, little or no leptin. Lipodystrophy is characterized by insulin resistance and fatty liver, which can be normalized with exogenous leptin treatment (36). Mice that have no leptin receptors within the brain are obese, insulin resistant, and have fatty livers, whereas mice with no peripheral receptors are normal (7). Leptin resistance is probably caused by an impaired transport across the blood-brain barrier which accompanies obesity and impaired receptor and postreceptor responses (6, 8, 9, 12, 37–41).

Reasons other than genetic predisposition could explain why some individuals in this study became obese. For example, younger animals, because of agility, or older animals, because of experience, might be able to take greater advantage of the garbage. However, animals in the Garbage HL group fell in the middle of the age range. Social rank might also be considered a predisposition, with baboons of higher social rank claiming more food or baboons of lower social rank expending fewer calories in defense of their social standing. But the Garbage HL baboons were evenly dispersed among the social rankings of their age-sex class. It should be noted that male baboons leave their original group shortly after reaching adulthood to immigrate to a new one. The two oldest of the Garbage group, which were LLs, probably joined the Garbage group at least 5 yr before the study. All of the other garbage-feeding baboons grew up in that group. Despite 5 yr of feeding as adult males in this artificially enriched environment, these animals had low serum leptin levels.

What factors may have accounted for the development of obesity and abnormal chemistries in these otherwise wild baboons? Obesity in humans is usually blamed on too little exercise, overeating, and too many calories from fats and simple sugars. Here, the diet of the garbage-feeding baboons had about the same fat content as the baboons feeding entirely on natural foods, and they consumed about the same number of calories. These results suggest that a high fat content in the diet is not critical to the development of obesity and syndrome X, but that these conditions can occur in susceptible individuals simply from a mismatch between calories ingested and calories expended. In particular, a decrease in activity levels was likely a key factor in the development of obesity and metabolic abnormalities.

In conclusion, we showed that baboons with access to the abundant and easily accessible food at a lodge and who, therefore, had reduced activity levels developed elevations in serum leptin, obesity, hyperlipidemia, and insulin resistance. However, obesity as measured by BMI, mass, and leptin developed in only a subset of the population and was accompanied by insulin resistance and hyperglycemia. This subset was not characterized by differences in social rank or age. Furthermore, the most severe cases of hyperlipidemia developed in a different subset. These findings show that in wild baboons, a syndrome X-like condition can develop in a subset of individuals in a sedentary population with access to excess calories.

Acknowledgments

We thank Kathy Wolf for technical assistance. Appreciation is due to the Office of the President, Republic of Kenya, to the Kenya Wildlife Services, its Amboseli staff and Wardens, the Institute of Primate Research, and the members of the Amboseli pastoralist community. Particular thanks goes to Amboseli Baboon Research Project co-director Susan Alberts and the Amboseli field workers who also contributed to sample and data collection—especially P. Muruthi, R. Mututua, and S. Sayialel. We thank J. W. Kemnitz and M. L. Stefanick and their laboratory staff for the cholesterol, insulin, and glucose values.

Received October 30, 2002. Accepted December 13, 2002.

Address all correspondence and requests for reprints to: William A. Banks, 915 North Grand Boulevard, St. Louis, Missouri 63106. E-mail: bankswa@slu.edu.

This work was supported by Veterans Affairs Merit Reviews (to W.A.B. and J.E.M.), National Institute of Neurological Disorders and Stroke Grant R01 NS41863 (to W.A.B.), National Institute on Alcohol Abuse and Alcoholism Grant R01 AA12743 (to W.A.B.), the Chicago Zoological Society (to J.A.), and National Science Foundation Grant IBN-9983910 and its predecessors (to J.A.).

References

1. **Friedman JM, Halaas JL** 1998 Leptin and the regulation of body weight in mammals. Nature 395:763–770
2. **Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM** 1995 Weight-reducing effects of the plasma protein encoded by the *obese* gene. Science 269:543–546
3. **Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM** 1996 Leptin enters the brain by a saturable system independent of insulin. Peptides 17:305–311
4. **Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P** 1995 Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science 269:546–549
5. **Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F** 1995 Effects of the *obese* gene product on body weight regulation in *ob/ob* mice. Science 269:540–543
6. **Banks WA, DiPalma CR, Farrell CL** 1999 Impaired transport of leptin across the blood-brain barrier in obesity. Peptides 20:1341–1345
7. **Cohen P, Zhao C, Cai X, Montez JM, Rohani SC, Feinstein P, Mombaerts P, Friedman JM** 2001 Selective deletion of leptin receptor in neurons leads to obesity. J Clin Invest 108:1113–1121
8. **Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM** 1997 Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci USA 94:8878–8883
9. **Kastin AJ, Pan W, Maness LM, Koletsky RJ, Ernsberger P** 1999 Decreased transport of leptin across the blood-brain barrier in rats lacking the short form of the leptin receptor. Peptides 20:1449–1453
10. **Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS** 1996 Role of leptin in the neuroendocrine response to feeding. Nature 382:250–252
11. **Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA, O'Rahilly S** 1999 Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 341:879–915
12. **Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, Lynn RB, Zhang PL, Sinha MD, Considine RV** 1996 Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 348:159–161
13. **Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte Jr D** 1996 Cerebrospinal fluid leptin levels: relationship to plasma levels and adiposity in humans. Nat Med 2:589–593
14. **Fujioka K, Murphy-Filkins R, Green D, DePaoli A, LeBel C,** Significant body composition changes observed in obese subjects receiving chronic subcutaneous administration of a modified form of recombinant human leptin. Annual Meeting of the North American Association for the Study of Obesity, Long Beach, CA, 2000 (Abstract O-117)
15. **Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, McCamish M** 1999 Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 282:1568–1575
16. **Spiegelman BM, Flier JS** 1996 Adipogenesis and obesity: rounding out the big picture. Cell 87:377–389
17. **Ahima RS, Dushay J, Flier SN, Prabakaran D, Flier JS** 1997 Leptin accelerates the onset of puberty in normal female mice. J Clin Invest 99:391–395
18. **Bouloumie A, Drexler HCA, Lafontan M, Busse R** 1998 Leptin, the product of Ob gene, promotes angiogenesis. Circ Res 83:1059–1066
19. **Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Bell FT, Shen J, Vinson C, Rueger JM, Karsenty G** 2000 Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell 100:197–207
20. **Martin-Romero C, Sanchez-Margalet V** 2002 Human leptin activated P13K and MAPK pathways in human peripheral blood mononuclear cells: possible role of Sam68. Cell Immunol 212:83–91
21. **Banks WA, Phillips-Conroy JE, Jolly CJ, Morley JE** 2001 Serum leptin levels in wild and captive populations of baboons (*Papio*): implications for the ancestral role of leptin. J Clin Endocrinol Metab 86:4315–4320
22. **Altmann J, Alberts SC, Haines SA, Dubach J, Muruthi P, Coote T, Geffen E, Cheesman DJ, Mututua RS, Saiyalel SN, Wayne RK, Lacy RC, Bruford MW** 1996 Social structure predicts genetic structure in a wild primate group. Proc Natl Acad Sci USA 93:5797–5801
23. **Altmann J, Muruthi P** 1988 Differences in daily life between semiprovisioned and wild-feeding baboons. Am J Primatol 15:213–221
24. **Altmann J, Schoeller D, Altmann SA, Muruthi P, Sapolsky RM** 1993 Body size and fatness of free-living baboons reflect food availability and activity levels. Amer J Primatol 30:149–161
25. **Hahn NE, Proulx D, Muruthi PM, Alberts S, Altmann J** Gastrointestinal parasites in free-ranging Kenyan baboons. Int J Primatol, in press
26. **Hausfater G** 1975 Dominance and reproduction in baboons: a quantitative analysis. Basel: Karger
27. **Alberts SC, Altmann J** 1995 Balancing cost and opportunities: dispersal in male baboons. Am Nat 145:279–306
28. **Alberts SC, Altmann J** 1995 Preparation and activation: determinants of age at reproductive maturity in male baboons. Behav Ecol Sociobiol 36:397–406
29. **Pereira ME** 1988 Agonistic interactions of juvenile savanna baboons I: fundamental features. Ethology 79:195–217
30. **Kemnitz JW, Sapolsky RM, Altmann J, Muruthi P, Mott GE, Stefanick ML** 2002 Effects of food availability on serum insulin and lipid concentrations in free-ranging baboons. Am J Primatol 57:13–19
31. **Warnick GR, Benderson J, Albers JJ** 1982 Dextran sulfate-Mg2+ precipitation for quantitation of high-density-lipoprotein cholesterol. Clin Chem 28:1379–1388
32. **Muruthi P, Altmann J, Altmann S** 1991 Resource base, parity, and reproductive condition affect females, feeding time and nutrient intake within and between groups of a baboon population. Oecologia 87:467–472
33. **Glassman DM, Coelho J** 1987 Principal components analysis of physical growth in savannah baboons. Am J Phys Anthropol 72:59–66
34. **Rutenberg GW, Coelho J, Lewis DS, Carey KD, McGill J** 1987 Body composition in baboons: evaluating a morphometric method. Am J Primatol 12: 275–285
35. **Banks WA, LeBel C** 2002 Strategies for the delivery of leptin to the CNS. J Drug Target 10:297–308
36. **Arioglu E, Simna V, Andewelt A, Ruiz E, Snelt, P, Reitman M, DiPaoli A, Wagner A, Taylor SI, Gordon P, Abhimanyu G,** Efficacy of leptin replacement in lipoatrophic diabetes. 61st Scientific Session of The American Diabetes Association, Philadelphia, PA, 2001 (Abstract)
37. **El Haschimi K, Pierroz DD, Hileman SM, Bjorbaek C, Flier JS** 2000 Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. J Clin Invest 105:1827–1832
38. **Banks WA, Niehoff ML, Martin D, Farrell CL** 2002 Leptin transport across the blood-brain barrier of the Koletsky rat is not mediated by a product of the leptin receptor gene. Brain Res 950:130–136
39. **Hileman SM, Pierroz DD, Masuzaki H, Bjorbaek C, El Haschimi K, Banks WA, Flier JS** 2002 Characterization of short isoforms of the leptin receptor in rat cerebral microvessels and of brain uptake of leptin in mouse models of obesity. Endocrinology 143:775–783
40. **Schwartz MW, Woods SC, Porte Jr D, Seeley RJ, Baskin DG** 2000 Central nervous system control of food intake. Nature 404:661–671
41. **van Heek M, Compton DS, France CF, Tedesco RP, Fawzi AB, Graziano MP, Sybertz EJ, Strader CD, Davis J** 1997 Diet-induced obese mice develop peripheral, but not central, resistance to leptin. J Clin Invest 99:385–390