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Leptin, Adiposity, and Testosterone in Captive Male Macaques

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ABSTRACT Leptin is considered to act as a signal relating somatic energetic status to the reproductive system. However, the nature of that signal and its relationship with male reproductive function across nonhuman primate species are unclear. We suggest that species-specific differences in leptin physiology may be related to the degree of environmental variation and variation in the importance of energy stores for male reproduction. In order to test the role of seasonality in species differences among nonhuman primates, we compared leptin, testosterone, and body composition in male rhesus (n = 69) and pig-tailed (n = 43) macaques. Despite having larger abdominal fat deposits, the rhesus macaques did not exhibit significantly higher leptin levels (rhesus, 2.21 ± 0.43 ng/ml; pig-tailed, 2.12 ± 0.39 ng/ml). Both species showed increases in leptin across adolescent, subadult, and adult age-groups ($P = 0.036$ for rhesus; $P = 0.0003$ for pig-tailed by ANCOVA). Testosterone was not significantly associated with leptin in either the rhesus ($r = 0.039$; $P = 0.754$) or pig-tailed ($r = 0.2862$; $P = 0.066$) samples. Comparison of leptin levels across the two species using univariate modeling procedures showed no significant age-group by abdominal fat interaction. These findings suggest little difference in leptin production between these two closely related species, despite the difference in breeding seasonality. Am J Phys Anthropol 127:335–341, 2005.

It is now well-accepted that whereas food resource distribution largely determines female dominance relationships and group size in nonhuman primates, male relationships and grouping patterns are determined by the distribution of females (Wrangham, 1980; van Hooff and van Schaik, 1994; van Schaik, 1996; Sterk et al., 1997). The temporal distribution of fertile females will influence the degree of male-male competition which may, in turn, affect the patterns of male reproductive and somatic development.

The socioendocrinology of mandrills (*Mandrillus sphinx*) provides one illustrative example of the effects of male-male competition on development (Setchell and Dixson, 2001), with adult males exhibiting morphological variants ranging between "fatted" individuals (with maximum secondary sexual coloration and large rumps) and "nonfatted" individuals (with muted secondary sexual adornments and slimmer rumps). Furthermore, in this species, different morphological variants tend to practice different reproductive strategies, from "fatted" males which engage in mate-guarding and intense male-male competition, to "nonfatted" males which are usually solitary or peripheral to the social group and practice opportunistic mating with no mate guarding (Dixson et al., 1993). In this case, suppression of the development of secondary sexual characteristics may function in part to reduce intermale competition, in turn facilitating alternative mating tactics (Setchell and Dixson, 2001, 2002), as seems also to be the case in orangutans (*Pongo pygmaeus*) (Maggioncalda et al., 1999, 2000).

Likewise, the degree of intrasexual competition for access to mates may also influence the timing of

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development in other cercopithecine species. Males of some species may develop early, bulking up and beginning to compete ("contest competition;" Sterk et al., 1997) with conspecifics for access to mates. Alternatively, males of some other species may postpone somatic development and develop fully only when the likelihood of male-male competition is relaxed.

Seasonal breeding is one potential factor in the timing of male reproductive maturation among cercopithecines. If breeding seasonality evolves in response to predictable seasonal energy shortfalls rather than female periovulatory synchronization due to potential single-male monopolization, then males (as well as females) may be selected to develop efficient fat deposition mechanisms quickly to help them get through inevitable lean times. This seems to be the case in ringtailed lemurs (*Lemur catta*), which grow amazingly fast, presumably because reaching relatively large size early helps them to survive their first dry season and to do well in competition for dominance (Pereira, 1993).

Although lemurs possess a long separate evolutionary history from cercopithecines, the same principle should apply to seasonally breeding macaques that face harsh seasonal conditions. In addition, males in seasonally breeding species mature in age cohorts, and thus will predictably have same-age competitors near them in the future. Therefore, early and rapid development may favor males that face inevitable competition among conspecifics.

This study attempts to more clearly identify the relationships between degree of male-male competition, somatic and reproductive development, and leptin levels in two different species of macaques that differ, in part, in their degree of breeding and birthing seasonality. We previously reported that a large sample of captive male rhesus macaques demonstrated significantly larger abdominal fat deposits than pig-tailed macaques (Muehlenbein et al., 2002). In addition, the rhesus showed signs of earlier reproductive maturation, as evidenced by larger testicular volume, higher testosterone levels, and greater crown-to-rump length among adolescents.

Given their greater amount of abdominal fat, we expected that the rhesus would also exhibit higher levels of leptin, a protein hormone produced by adipocytes that has evolved to maintain energy homeostasis (Casanueva and Dieguez, 1999) by informing the hypothalamus about the status of fat stores or changing body composition (Suter et al., 2000). However, since leptin infusion does not affect luteinizing hormone, testosterone, or cortisol levels in food-restricted adolescents (Lado-Abeal et al., 1999) and adults (Lado-Abeal et al., 2000), we expected to find no relationship between testosterone and leptin in both species.

SPECIFIC HYPOTHESES

1. Leptin levels will be higher in rhesus than pig-tailed macaques as a function of differences in abdominal fat levels.
2. Leptin levels will not be related to testosterone levels in both species.

METHODS

This cross-sectional survey utilized 69 male rhesus macaques of Indian origin between 3–14 years of age and 43 male pig-tailed macaques between 3–12 years of age, maintained at the Tulane National Primate Research Center. Rhesus macaques are multimale, multifemale breeders, which are highly seasonal in breeding and birthing in both captive and natural settings (Conaway and Koford, 1964; Drickamer, 1974; Wilson et al., 1978), and males reach sexual maturity within 3–5 years of life (Napier and Napier, 1985). In contrast, pig-tailed macaques (*Macaca nemestrina*) demonstrate a polygamous, multimale nonseasonal breeding system, where estrous females are present year-round in the group (Caldecott, 1986; Oi, 1996). Pig-tailed macaque males reach sexual maturity within 3–4.5 years of life (Sirianni and Swindler, 1985).

Animals were housed in one-half and one-quarter acre corrals as well as corncribs and individual restraining cages. Of the 43 pig-tailed macaques used, 35 were housed in outdoor corrals (0.003–0.006 animals per square foot), 7 in individual cages (0.233 animals/ft^2), and one in a corncrib (0.063 animals/ft^2). Of the 69 rhesus macaques, 49 were housed in outdoor corrals (0.0007–0.008 animals/ft^2), 14 in individual cages (0.233 animals/ft^2), and 6 in corncribs (0.04–0.08 animals/ft^2). Cage sizes are reported for accurate representation of data. There was no statistically significant ($P \leq 0.05$) influence of particular cage size in any of the following analyses. Cage size information will therefore no longer be reported. In general, the corrals demonstrate a consistent and seminatural ecological context (Sade, 1964). All measurements took place between October 1998–January 1999, the rhesus' common breeding season.

All animals were provisioned with Purina Monkey Chow (Ralston Purina Co., St. Louis, MO) daily. Amount of chow distributed was determined by the number of animals in each enclosure (approximately one 50-lb bag per 30 animals). According to the manufacturer, this diet is low in fat (crude fat, 5% minimum) and high in protein (crude protein, 20% minimum). Diet was supplemented with fresh fruit weekly, and water was available ad libitum. On the days the sampling was done, the animals were not provided with the standard ration of monkey chow until after the samples were drawn. Matrilineal data and precise chronological ages were maintained in the Center's computer system. In order to minimize interobservational error, morphometric measurements were made by one investigator (M.P.M.) when possible. However, a small number (<10%) were made by another trained investigator (M.A.M.).

All animals were anesthetized with ketamine hydrochloride (10 mg/kg), a dissociative anesthetic that has not demonstrated any significant effects on serum androgen levels or production rates (Zaidi et al., 1982). Each animal was examined once, between 8:00–10:30 hr, to eliminate any circadian effect. All animals were held in a standardized position, with their bodies lying on the left side and arms and legs extended perpendicular to the vertebral axis. The head and muzzle were aligned in the Frankfort plane relative to the torso (Coelho, 1985). Body weight was determined to the nearest 0.1 kg. A Dean fiberglass tape measure was placed parallel to the vertebrate column and measured to the nearest 0.1 cm from the occipital node to the ischeal callosity. The upper arm circumference, a good predictor of lean body mass (Schwartz and Kemnitz, 1992), was measured to the nearest 0.1 cm by wrapping the tape measure around the halfway point between the olecranon and the tip of the scromion.

Tricep skinfold was measured to the nearest millimeter using nonflexible, sliding calipers; the periumbilicular (abdominal) skinfold was measured 1 cm below the umbilicus; and the subscapular skinfold was measured 1 cm below the inferior angle of the scapula (Coelho, 1985). Past studies indicated that abdominal skinfold in male rhesus macaques is significantly correlated with amount of total body fat (Kemnitz and Franken, 1986). In addition, primate mass index (PMI) was calculated as weight (kg) divided by crown-rump length squared (m^2). Unlike the body mass index (BMI) traditionally used in humans, this measure does not take into account lower limbs, but is used similarly as a relative measure of body mass. Furthermore, PMI is not used as an index of fatness per se, but rather as a measure of relative size used in addition to length, weight, and skinfolds.

For each animal, a blood sample was collected from the femoral vein, using a 4-ml SST Vacutainer Collection Tube with serum separator (Beckton-Dickinson, Franklin Lakes, NJ) and a 21-gauge needle. These blood samples were collected immediately following tranquilization, in order to minimize capture stress from significantly influencing gonadal and adrenal hormone concentrations (Sapolsky, 1986). Sera were stored at −40°C and assayed for total testosterone using solid-phase ^{125}I radioimmunoassay procedures (Diagnostic Products Corp., Los Angeles, CA). Leptin levels were determined using a nonhuman primate-specific RIA kit by Linco Research, Inc. (St. Charles, MO). Intraassay coefficients of variation were less than 5.9% for all assays.

Macaques were assigned to age groups on the basis of the previously established age categories outlined below (Muehlenbein et al., 2002):

Age group 1: Ages 3.5–5.0 (adolescents), 17 rhesus; 22 pig-tailed;

Age group 2: Ages 5.1–8.9 (subadults), 27 rhesus; 10 pig-tailed; and

Age group 3: Ages 9.0–15.0 (prime adults), 25 rhesus; 11 pig-tailed.

The Statistical Package for the Social Sciences (SPSS), version 10.0 for Macintosh, was used to determine differences between species (all ages collapsed) via ANCOVA, controlling for age. Bivariate associations between hormonal and morphometric factors were assessed using Pearson's correlation coefficients. Partial correlation coefficients were also computed, controlling for age.

Differences between average hormonal and morphometric variables for each species and age group were assessed using ANOVA. Differences in average leptin values (± SEM) between individual macaque age-groups were assessed using the LSD post hoc test.

RESULTS

Average values

Because the average age of the rhesus sample was slightly older than the pig-tailed, we used ANOVA (with species as a fixed variable and age as a covariate) to test for differences across the two species. Consistent with what we described earlier from a smaller sample (Muehlenbein et al., 2002), rhesus macaques had more abdominal fat (rhesus, 15.88 ± 1.15 mm; pig-tailed, 9.02 ± 1.18 mm) and a lower PMI (rhesus, 46.50 ± 0.98 kg/m^2; pig-tailed, 50.63 ± 1.62 kg/m^2) than the pig-tailed macaques. The two macaque species did not significantly differ in triceps circumference, triceps skinfolds, length, or weight (results not shown).

Comparing hormonal values across the two species, there were no significant differences in either leptin (rhesus, 2.21 ± 0.43 ng/ml; pig-tailed, 2.12 ± 0.39 ng/ml) or testosterone (rhesus, 4.63 ± 0.38 ng/ml; pig-tailed, 3.53 ± 0.49 ng/ml).

Seasonal variation

As discussed above, measurements were collected from the beginning to the middle of the rhesus breeding season. Given morphological and hormonal changes during the breeding season (Bercovitch, 1989), changes within the rhesus may have confounded differences between the species. Additionally, changes in leptin across the breeding season might have distorted the relationship between hormonal and morphometric variables within the rhesus themselves. Therefore, partial correlations between leptin and time of data collection (dates collapsed into week intervals; weeks 1–8 for the rhesus, and 9–12 for the pig-tailed) among macaque species were employed while controlling for age and PMI. Among the rhesus, week of data collection was not correlated with leptin when controlling for age and PMI ($r = 0.1623$; $P = 0.190$). Likewise, there was no significant correlation of week with leptin in the pig-tailed sample when controlling for age and PMI ($r = 0.0374$; $P = 0.816$). Thus, our sampling regime did not confound potential differences in leptin levels within and between species, and week of

TABLE 1. Correlations of morphometric and hormonal variables to leptin[1]

	Rhesus (N = 69)	Pig-tailed (N = 43)
Age (years)	0.2529*	0.4421**
Weight (kg)	0.5686**	0.5195**
Length (cm)	0.2088	0.4021**
PMI (kg/m^2)	0.5591**	0.3393*
Abdominal fat (mm)	0.5957**	0.5787**
Testosterone (ng/ml)	0.0390	0.2862

[1] Partial correlation coefficients when controlling for age. PMI, primate mass index.
* $p < 0.05$.
** $p < 0.01$.

sampling was not included as a control in subsequent analyses.

Correlations between leptin, testosterone, and body composition

Using partial correlation analyses controlling for age, leptin was significantly associated with age, weight, PMI, and abdominal fat deposits in both species (Table 1). However, testosterone was not significantly associated with leptin in either the rhesus (r = 0.039; *P* = 0.754) or pig-tailed (r = 0.2862; *P* = 0.066) samples.

Age patterns of leptin levels

Figure 1 shows leptin levels by age group for the two species. For the rhesus sample, there was a significant (*P* = 0.036) increase in leptin levels throughout the age groups. In group contrasts, adolescent animals had significantly lower leptin levels (0.47 ± 0.02 ng/ml) than prime adults (3.36 ± 0.87 ng/ml) (*P* = 0.010), while neither the adolescent vs. subadult comparison (2.23 ± 0.70 ng/ml) (*P* = 0.107) nor the subadult vs. prime adult comparison (*P* = 0.245) showed significant differences. For the pig-tailed sample, there was also a significant (*P* = 0.003) increase in leptin levels throughout the age groups. The adolescents (0.91 ± 0.14 ng/ml) had significantly lower leptin levels as compared to both the subadult (3.48 ± 1.28 ng/ml) (*P* = 0.005) and prime adult (3.31 ± 0.64 ng/ml) (*P* = 0.006) groups. However, the subadult and prime adult groups did not significantly differ (*P* = 0.860).

Because of the intimate association of leptin and adiposity (Lonnqvist et al., 1997), additional analyses were undertaken to determine if differences in leptin by age group were related to differences in adiposity within each species. When PMI was included as a covariate in the macaque ANCOVAs, significant differences in leptin levels between age groups (within each species) disappeared. For the rhesus sample, there was no longer a significant effect of age group (*P* = 0.476), and the adolescent group no longer had a lower average leptin level compared to the prime adult group (*P* = 0.460). Likewise, for the pig-tailed sample, there were no significant age-group differences (*P* = 0.235), including differences between adolescents and subadults (*P* = 0.760) and adolescents and prime adults (*P* = 0.478).

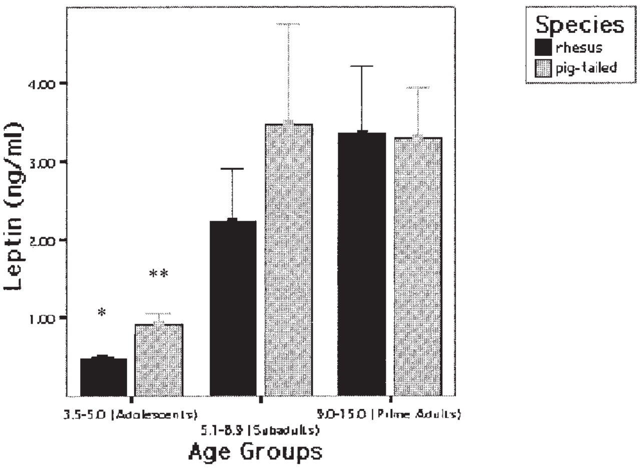

Fig. 1. Age-related changes in leptin levels in rhesus and pig-tailed macaques. Average leptin levels (± SEM) by categories corresponding to major phases of macaque life cycle. *Significant difference between adolescent (0.47 ± 0.02 ng/ml) and prime-adult (3.36 ± 0.87 ng/ml) (*P* = 0.010) rhesus macaques as determined by univariate ANOVA. **Significant difference between adolescent (0.91 ± 0.14 ng/ml) and both subadult (3.48 ± 1.28 ng/ml) (*P* = 0.005) and prime-adult (3.31 ± 0.64 ng/ml) (*P* = 0.006) pig-tailed macaques as determined by univariate ANOVA. GLM univariate modeling procedures, controlling for either PMI or abdominal fat differences between the two species (univariate ANOVA with species and age group as fixed variables, and PMI or abdominal fat as covariates), revealed no significant species-by-age-group interactions (*P* = 0.057 and *P* = 0.101, respectively), indicating approximately parallel changes in leptin by age in the two species.

However, when abdominal fat was included as a covariate in the macaque ANCOVAs, different results were obtained for the two species. For the rhesus sample, there was no longer a significant effect of age group (*P* = 0.860), and the adolescent group no longer had a lower average leptin level compared to the prime-adult group (*P* = 0.908). On the other hand, for the pig-tailed sample, age group (*P* = 0.017) remained a significant predictor, while the contrast between the adolescent and subadult groups (*P* = 0.070) remained marginal, and that between the adolescent and prime-adult groups was independent of leptin (*P* = 0.811).

In order to investigate these apparent species difference in the relationship of age-related changes in leptin with age-related changes in adiposity, we used univariate modeling procedures (generalized linear model: GLM), controlling for PMI differences between the two species (univariate ANOVA with species and age group as fixed variables, and PMI as a covariate). The results revealed a marginal species-by-age-group interaction (*P* = 0.057), suggesting that leptin levels might vary between the two species independent of body composition. However, when controlling for abdominal fat differences between the two species (univariate ANOVA with species and age group as fixed variables and abdominal fat as a covariate), there was no significant species-by-age-group interaction ($P = 0.101$). This suggests that differences in age-related patterns of leptin can be related to species differences in age-related patterns of abdominal fat (Muehlenbein et al., 2002).

DISCUSSION

The results presented here indicate that: 1) leptin increases with both adiposity and age within both male rhesus and pig-tailed macaques; 2) apparent species differences in age-related patterns of leptin levels are a consequence of species differences in age patterns of abdominal fat; and 3) leptin levels show no association with testosterone. These results suggest that earlier somatic maturation among rhesus compared to pig-tailed macaques (Muehlenbein et al., 2002) is related to increased abdominal fat stores, but earlier reproductive maturation does not appear to be mediated directly by increased levels of leptin.

Increased subcutaneous abdominal fat among young rhesus compared to pig-tailed macaques may reflect the evolutionary ecology of rhesus macaques as seasonal breeders in response to fluctuation in food availability. Thus rhesus males may have been selected to respond to weight changes over the course of the breeding season. Abdominal fat is thought to be easily mobilized (Pond, 1998), and thus can act as short-term energy storage for males that experience negative energy balance and weight loss during a restricted breeding season (Muehlenbein et al., 2002).

Relationships of leptin to body composition

All deposits of white adipocytes are capable of synthesizing and secreting leptin (Zhang et al., 1994; Masuzaki et al., 1995; Lonngvist et al., 1997). However, adipose tissue in varying locations responds differently to androgens, estrogens, and glucocorticoids (Russel et al., 1998). Thus, both species-specific differences in the distribution of subcutaneous abdominal adipose tissue and its sensitivity to steroid hormones (among other factors) might help account for species differences in the relationship of leptin to measures of adiposity. The finding that a species-by-age-group interaction was not a significant predictor of leptin levels when controlling for abdominal fat suggests that differences in age-related changes of leptin between rhesus and pig-tailed macaques are directly related to species differences in body composition with age.

Relationships of leptin to gonadal function

These results show no relationship between leptin and testosterone in either of the two species examined (Table 1). This is consistent with earlier results indicating no association between testosterone and leptin levels in the adolescent rhesus (Mann et al., 2000), as well as findings that acute leptin infusion did not affect luteinizing hormone, testosterone, or cortisol levels in food-restricted adolescent (Lado-Abeal et al., 1999) and adult (Lado-Abeal et al., 2000) male rhesus. Together these results suggest that leptin does not play a direct role in modulating the hypothalamic-pituitary-testicular axis in nonhuman primates, as it appears to do in rodents. Among rodents, leptin has direct effects on testicular steroidogenesis (Tena-Sempere et al., 1999), testes and seminal vesicle size and sperm counts (Barash et al., 1996), and luteinizing hormone and follicle-stimulating hormone release from rat testicular tissue in vitro (Yu et al., 1997).

In humans, an inverse relationship between leptin and testosterone levels was reported (Behre et al., 1997; Jockenhovel et al., 1997; Pineiro et al., 1999; Horlick et al., 2000), consistent with the lipolytic effects of androgens. However, both men from non-Western human populations (Luke et al., 1998; Bribiescas, 2001) and wild baboons (Banks et al., 2001) exhibit significantly lower leptin levels than their better-fed Western or captive counterparts. Thus the high levels of leptin and their negative association with testosterone in well-fed human populations may provide a misleading picture of leptin's functional effects on the male reproductive system.

The leptin levels reported here are in the range of those evidenced by captive baboons (Banks et al., 2001), suggesting that a similar caveat is necessary before interpreting our results as necessarily species-typical for either rhesus or pig-tailed macaques. Further studies are needed in order to determine if our current findings can be generalized to wild populations of macaques.

CONCLUSIONS

The results of this study indicate little difference in leptin levels or the relationship between leptin and adiposity between rhesus and pig-tailed macaques. Importantly, this is despite the fact that the two species differ in adiposity: pig-tailed macaques have more subscapular fat, and rhesus macaques have more abdominal, subcutaneous fat. Furthermore, species differences in abdominal fat alone appear sufficient to account for species differences in age-related patterns of leptin. The fact that both species of macaques failed to exhibit a relationship between leptin and testosterone similar to that found in humans suggests that the role of leptin in male reproductive function may differ between human and captive, provisioned nonhuman primate populations. Further studies in wild and captive primates, especially great apes, are necessary to prove such a conclusion.

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