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Serum Leptin Levels and Anthropometric Correlates in Ache Amerindians of Eastern Paraguay

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KEY WORDS reproductive ecology; body composition; sexual dimorphism; peptide hormone; endocrinology; Indians; South America

ABSTRACT Leptin is a recently discovered peptide hormone secreted primarily from adipocytes in humans and other mammals; it is a reflection of fat stores, and has been associated with reproductive function. However, few leptin measurements are available from nonindustrialized populations, including contemporary hunter/gatherer communities undergoing the transition to sedentary agriculture. This investigation reports single-sample serum leptin measurements in healthy Ache Amerindian males (n = 21; average age, 32.8 ± 3.4 SE) and females (n = 12; average age, 31.3 ± 4.3) in eastern Paraguay. Ache leptin concentrations were much lower than in industrialized populations, although significant sexual dimorphism was evident (female 5.64 ng/ml ± 0.91 SE vs. male 1.13 ng/ml ± 0.08; $P < 0.0001$). Indeed, female leptin levels were similar to those of anorexic women, despite apparently adequate adiposity. Controlling for fat percentage, no significant sex difference was evident, suggesting that adiposity was the primary source of leptin variation. Body fat percentage was highly correlated with leptin in females ($r^2 = 0.72$; $P < 0.0005$) but not males, who exhibited a modest negative correlation ($r^2 = 0.25$; $P < 0.03$). Weight ($r^2 = 0.45$; $P = 0.02$) and BMI (kg/m^2) ($r^2 = 0.81$; $P < 0.0001$) were also significantly correlated in females but not males. These results suggest that: 1) clinical leptin norms based on industrialized populations may represent the highest range of human variation and may not be representative of most human populations; 2) hormonal priming may underlie population variation in leptin profiles; and 3) the relative importance of leptin as a proximate mechanism regulating reproductive effort during human evolution may have been modest. Am J Phys Anthropol 115:297–303, 2001.
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Accurate assessments of somatic condition are essential to life history research, and it has been suggested that hormone function is a key proximate mechanism controlling life history tradeoffs in a variety of organisms, including humans (Bribiescas, 1997; Ellison, 1990; Ketterson and Nolan, 1999; Stearns, 1989). Although skinfold and other anthropometric assessments are useful indicators of somatic composition in human populations, measurements of proximate factors that directly reflect energy reserves, in particular fat stores, have been elusive. Leptin is a recently discovered polypeptide hormone secreted in mammals primarily by adipocytes (Friedman and Halaas, 1998; Rosenbaum et al., 1996), and is a direct endocrine reporter of fat reserves to the hypothalamus (Casanueva and Dieguez, 1999; Wurtman, 1996). Given the central role of leptin as a fat reporter to the brain and other tissues , leptin can be of tremendous use to evolutionary human biology research.

Leptin has been associated with reproductive endocrine function, with leptin levels varying with fecundity and reproductive maturation in female mice (Cheung et al., 1997), although the role of leptin in human reproduction is still under intense investigation (Barash et al., 1996). Sexual dimorphism in humans has been reported (Garcia-Mayor et al., 1997; Havel et al., 1996; Saad et al., 1997), with leptin levels declining in males in association with adolescent rises in testosterone. In contrast, female leptin titers increase with higher estrogen titers during and after puberty (Garcia-Mayor et al., 1997). Adult leptin variation is primarily a function of adipose tissue percentage and age, with women exhibiting a decline in leptin concentrations after menopause (Rosenbaum et al., 1996). However, after controlling for body fat, postmenopausal women had significantly higher leptin levels compared to age matched males (Saad et al., 1997).

With few exceptions (Banerji et al., 1999; Ho et al., 1999; Luke et al., 1998; Perez-Bravo et al., 1998; Santos et al., 2000; Sheu et al., 1999), research on human leptin physiology has been limited to urban populations within the United States and Europe and has not encompassed the full range of human variation. Although clinical research has provided valuable insights into the overall physiology of lep-

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tin, previous anthropological research has shown that industrialized populations may represent one extreme of endocrinological variance and may not be reflective of the full range of human physiological diversity (Bribiescas, 1996, 1997; Ellison, 1994; Ellison et al., 1993). Indeed, this variance may reflect an adaptive response to efficiently allocate energetic resources between the needs of growth, maintenance, and reproduction (Bribiescas, 1996, 2001; Ellison, 1990).

The unique information provided by contemporary hunter/gatherers is especially important to biological anthropologists and those interested in the life history of human evolution (Bentley, 1999; Hill, 1993). Human evolution has occurred largely under the ecological context of hunting and gathering, and thus forager populations and those undergoing the transition to sedentary agriculture, such as the Ache, can provide important insights into the relationship between foraging ecologies and the physiological mechanisms that have evolved to cope with energy allocation decisions. As a direct mechanism involved with reporting available energy stores to the hypothalamus and reproductive system (Casanueva and Dieguez, 1999), documenting and comparing the patterns of leptin variation among contemporary foragers such as the Ache could be of great value to biological anthropologists and shed light on the physiological responses of our hominid ancestors to ecological challenges. This investigation reports leptin levels in Ache males and females, examined in the light of anthropometric data.

METHODS

Subjects

The Ache are an Amerindian population living in eastern Paraguay who subsist on foraged forest food products and limited farming (for a review of Ache history and ethnography, see Clastres, 1998; Hill and Hurtado, 1995). The community in this study are known as the Ñacunday Ache and, until the late 1970s, they subsisted on full-time forest foraging, but now live primarily through farming on the Protestant mission of Puerto Barra, approximately 100 km south of the city of Cuidad del Este in the province of Alto Parana. The total community numbers around 40 and consists of approximately a dozen households and a small government school. More detailed descriptions and analyses of Ache ecology and demography are available elsewhere (Hill and Hurtado, 1989, 1995).

Blood samples were collected from healthy male and female volunteers in exchange for a communal gift (male, n = 21; mean age, 32.8 ± 3.4 SE; female n = 12; mean age, 31.3 ± 4.3). Subjects were interviewed and screened for endocrine disorders or acute conditions such as pneumonia or upper respiratory infections. The collection protocol and subject recruitment methods were approved by the Yale University Faculty of Arts and Science Committee on Research Involving Human Subjects.

Hormonal measurement

Approximately 4 ml of blood were collected in SST vacuum tubes pretreated with a chemical clotting activator (Vacutainer #6514, Becton-Dickinson, Franklin Lakes, NJ) (Laessig et al., 1976; Reinartz et al., 1993), using standard phlebotomy methods, between 10 AM–12 PM. Although diurnal fluctuations in leptin have been noted (Sinha et al., 1996), this pattern seems to be the result of meal schedules (Schoeller et al., 1997). Most subjects had eaten their morning meal but not lunch. Blood samples were stored in an ice cooler with blue ice packs at 4°C for 5–6 hr until serum had separated from clot. This was well within the time range recommended for serum/clot contact time (Zhang et al., 1998). Serum was then extracted using a Pasteur pipette, stored in a 12 × 75 mm polystyrene tube, and kept frozen in a propane powered freezer at −20°C for 3 weeks until transportation to the Reproductive Ecology Laboratory at Yale University. Transportation involved storage of frozen samples in a cooler with blue ice packs for a period of approximately 24 hr until arrival at Yale University. Although samples thawed during transport, storage temperature was maintained at approximately 4°C. This is well within the tolerance limits for serum storage as outlined by the manufacturer of the leptin assay kit (Linco Research, Inc., St. Charles, MO).

Serum leptin was measured using an Iodine 125-based double-antibody radioimmunoassay kit (catalog no. HL-81K, Linco Research, Inc.). Quality control (QC) measurements were 2.84 and 18.63 ng/ml for QCs 1 and 2, respectively, which were well within the expected ranges outlined by the manufacturer. Key standard curve binding percentages, ED 20 = 24.97, ED 50 = 4.64, and ED 80 = 0.94, were also within the assay performance specifications. Final values were calculated using AssayZap 2.5 radioimmunoassay analysis software for Macintosh (Biosoft, Inc., Cambridge, UK).

Anthropometric measurements

Height was recorded to the nearest 0.1 cm on a concrete surface, using a standard anthropometer. Weight and body fat percentage were determined using a portable scale/bioelectric impedance fat meter to the nearest 0.1 kg and 0.1% body fat, respectively (TBF-551 Body Fat Monitor/Scale, Tanita Corporation of America, Inc., Arlington Heights, IL) (Jebb et al., 2000). Body mass index (BMI) was calculated using the standard formula of weight/height^2 (kg/m^2).

Statistical analysis

Differences between male and female leptin levels and ages were determined using Mann-Whitney U-tests. Anthropometric comparisons were conducted

TABLE 1. Summary of leptin and anthropometric results

	Age		Leptin (ng/ml)		Fat %		BMI		Weight (kg)		Height (cm)	
	F	M	F	M	F	M	F	M	F	M	F	M
Mean	32.2	32.8	5.64	1.13	33.3	17.9	25.2	23.8	55.2	56.3	147.6	153.8
SD	14.0	15.7	3.16	0.37	4.4	1.8	1.9	1.4	7.4	5.4	5.4	5.8
SE	4.0	3.4	0.91	0.08	1.3	0.4	0.5	0.3	2.1	1.2	1.6	1.3
Count	12.0	21.0	12.0	21.0	12.0	19.0	12.0	19.0	12.0	19.0	12.0	19.0
Minimum	14.0	13.0	1.74	0.76	27.0	14.6	22.9	21.3	45.2	48.3	140.5	141.3
Maximum	50.0	64.0	12.80	2.45	40.7	20.5	29.6	25.5	70.6	66.0	159.0	162.2

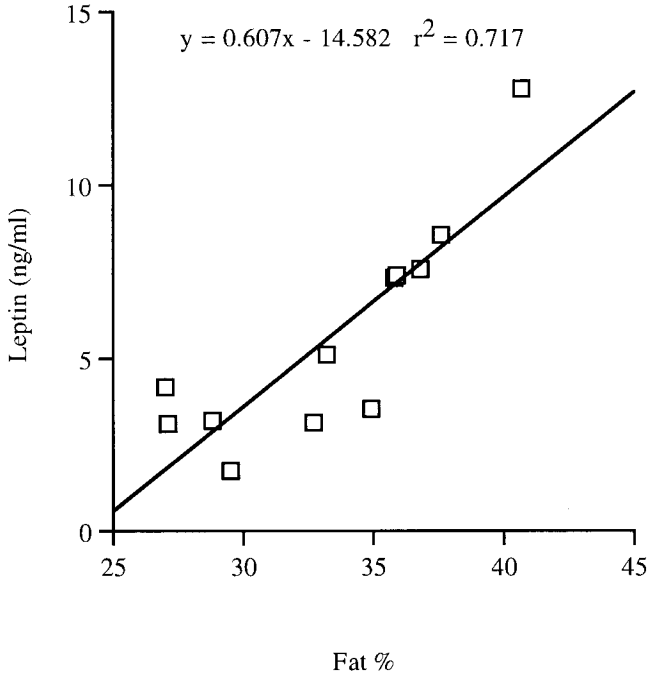

Fig. 1. Serum leptin levels in Ache females are significantly correlated with fat %, as determined by bioelectric impedance measures ($r^2 = 0.72$; $P < 0.0005$).

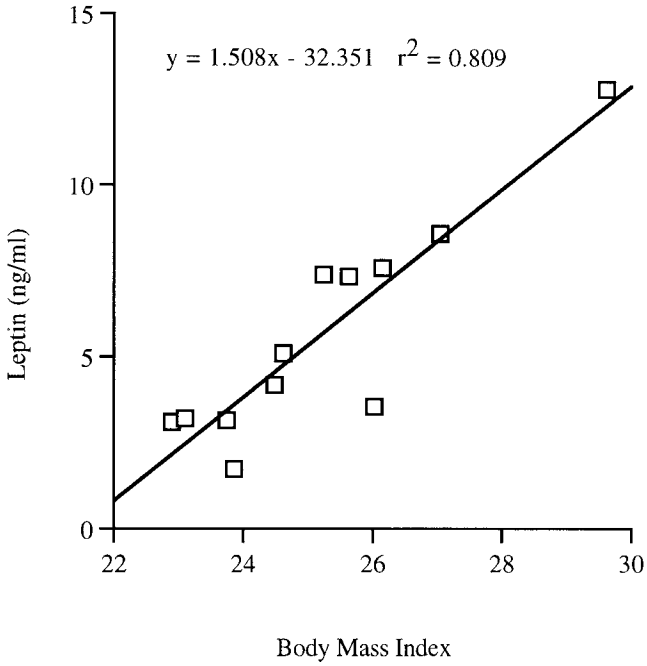

Fig. 2. Serum leptin levels in Ache females are significantly correlated with BMI (kg/cm^2) ($r^2 = 0.81$; $P < 0.0001$).

using unpaired *t*-tests, due to the parametric distribution of the data. Relationships between anthropometrics, age, and leptin levels were determined using Pearson's product moment correlation. Unpaired *t*-tests of linear regression residuals were used for between-sex comparisons that controlled for fat percentage, body size, and age. Results were analyzed using StatView 4.5 for Macintosh (Abacus Concepts, Inc., Berkeley, CA) and were considered significant at the 0.05 level.

RESULTS

Ache females exhibited a mean leptin concentration of 5.64 ± 0.91 SE ng/ml, which is extremely low compared to other populations (Table 1). Although fat ($r^2 = 0.72$; $P < 0.0005$) (Fig. 1), BMI ($r^2 = 0.81$; $P < 0.0001$) (Fig. 2), and weight ($r^2 = 0.45$; $P = 0.02$) (Fig. 3) were significantly correlated with leptin titers, Ache female leptin levels were similar to those of anorexic American women (Grinspoon et al., 1996), even though Ache women have significantly more fat (Fig. 4). Also of interest is one Ache woman (age 19), 9 months pregnant at the time of sampling, who exhibited the second highest leptin measurement of the study (7.4 ng/ml). This is in accordance with higher leptin levels in Western pregnant women, most likely due to increased pregnancy adiposity, although there is some dissociation between the rate of adipose tissue deposition and leptin increases (Butte et al., 1997; Hardie et al., 1997). However, the titer presented by the pregnant Ache woman is extremely low compared to other reports of leptin concentrations in Western pregnant women (Butte et al., 1997; Hardie et al., 1997).

Male leptin levels were significantly lower than those of females ($P < 0.0001$) (Fig. 5), similar to leptin sexual dimorphism in American populations (Havel et al., 1996; Saad et al., 1997). Controlling for body fat, sex differences in mean leptin levels were not significant ($P = 0.52$), suggesting that adiposity was the primary factor underlying sex differences in leptin. However despite strong correlations between fat percentage and leptin in females, males displayed only a modest negative trend ($r^2 = 0.25$; $P < 0.03$), although the association dissipated with the elimination of an outlier ($r^2 = 0.11$; $P < 0.19$). Weight ($r^2 = 0.11$; $P = 0.17$) and BMI ($r^2 = 0.03$; $P = 0.50$) also failed to correlate with leptin in Ache

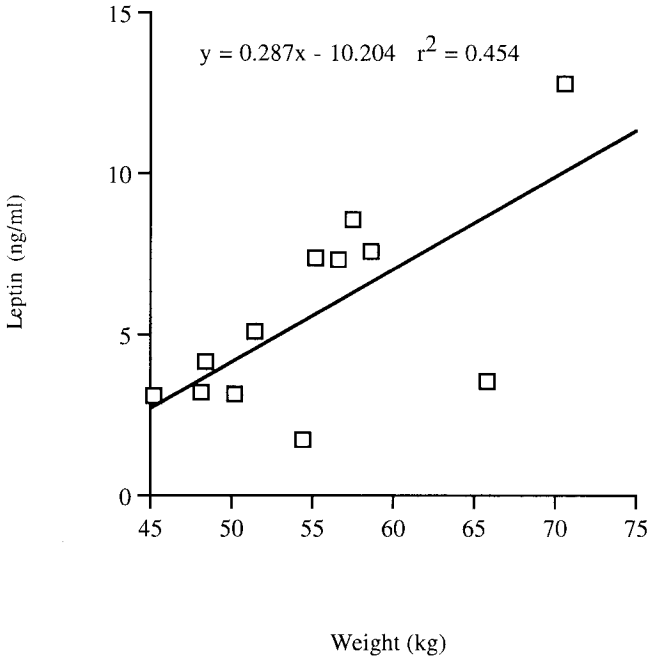

Fig. 3. Serum leptin levels in Ache females are significantly correlated with weight (kg) ($r^2 = 0.45$; $P = 0.02$).

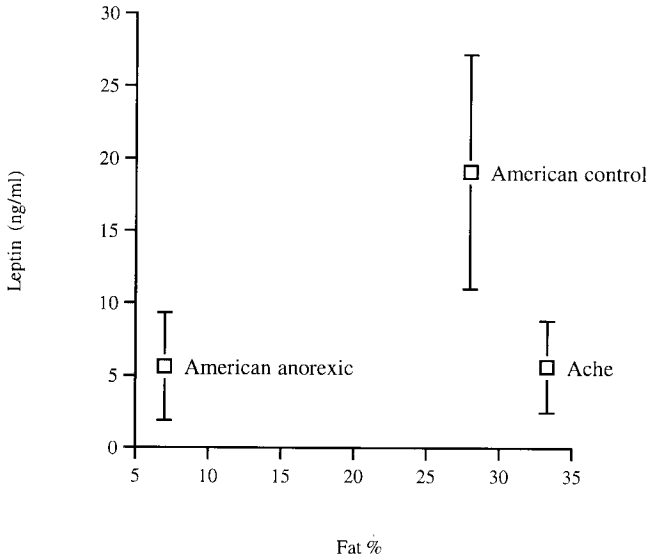

Fig. 4. Ache female leptin levels (n = 12; leptin = 5.6 ng/ml ± 3.2 SD; fat % = 33.3 ± 4.4) were comparable to American anorexic patients (n = 22; leptin = 5.6 ± 3.7; fat % = 7.0 ± 2.0) despite greater adiposity, similar to American controls (n = 23; leptin = 19.1 ± 8.1; fat % = 28.0 ± 5.0) (Grinspoon et al., 1996).

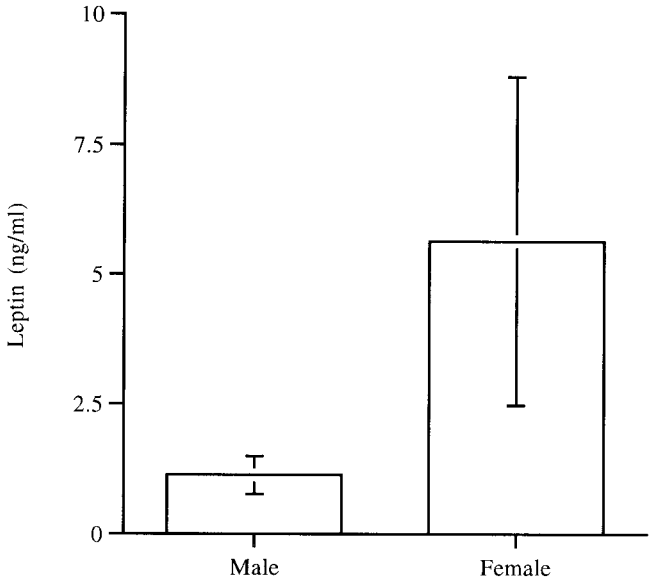

Fig. 5. Mean leptin differences between Ache males and females (Mann-Whitney U-test = 1.0; $P < 0.0001$).

males, contrasting with Western populations where leptin seems to be associated with adiposity in even the leanest men (Hickey et al., 1996). Indeed, clinical studies with comparable sample sizes of lean men have commonly reported a significant association between body composition and leptin (Elias et al., 2000; Gippini et al., 1999; Leal-Cerro et al., 1998; Rosenbaum et al., 1997). Sexually dimorphic leptin concentrations have been reported to persist in older men and postmenopausal women (Rosenbaum et al., 1996). However, age did not correlate with leptin levels among Ache males or females, even when controlling for fat percentage. Sample sizes were inadequate to determine age-specific differences in leptin levels between males and females, although age was not significantly correlated with leptin levels when sexes were pooled.

An examination of other populations, including the Ache, reveals a wide range of variation of mean leptin concentrations. For example, leptin concentrations in African-Americans, Jamaicans of African descent, and Nigerians revealed significant differences between these populations, suggesting that chronic environmental factors can play an important role in leptin variation. Nonetheless, across all of these populations, significant sexual dimorphism was evident, suggesting that sex differences in leptin concentrations are a common trait across populations and are relatively invariant (Luke et al., 1998). Leptin concentrations in African-American men were higher than levels found in Ache women, suggesting that sexually dimorphic differences are population specific (Fig. 6).

Finally, sexually dimorphic anthropometric differences included height ($P = 0.006$), fat percentage ($P < 0.0001$), and BMI ($P = 0.02$), but not weight ($P = 0.64$), suggesting that somatic composition is the key delineating factor in Ache subjects. This is in accordance with limited weight sexual dimorphism in the Northern Ache noted by Hill and Hurtado (1995). There was no significant difference in age between male and female subjects ($P = 0.94$).

DISCUSSION

Low leptin levels in Ache females, despite apparently adequate adiposity as well as the lack of somatic associations with leptin in Ache males, may be

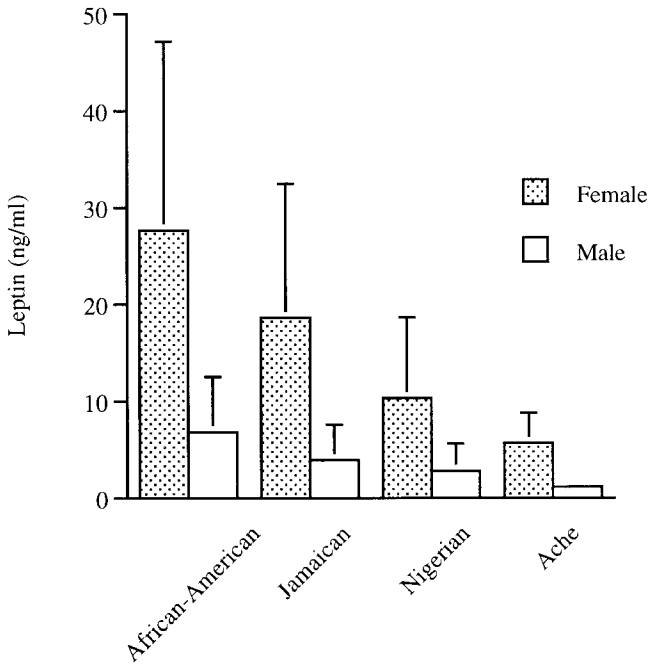

Fig. 6. Leptin concentrations (mean ± SD) are compared between four populations (African-American males, n = 275; females, n = 424; Jamaican males, n = 144; females, n = 226; Nigerian males, n = 175; females, n = 188; Luke, et al., 1998; Ache males, n = 21; females, n = 12; this study) in which leptin levels were assessed using the same assay (catalog no. HL-81K, Linco Research), illustrating significant population variation independent of adiposity.

due to different factors, including developmental priming, acute differences in diet or activity, genetic polymorphisms of the leptin molecule or receptor, or errors in field collection methodology. Receptor priming due to environmental differences prior to or during adolescence has been demonstrated to permanently affect hormonal function in later life. For example in men with idiopathic hypogonadotropic hypogonadism (IHH), a congenital hypothalamic inability to transcribe and secrete GnRH, patients who are exposed to endogenous GnRH during adolescence are more responsive to postadolescent GnRH treatment (Spratt and Crowley, 1988). Testicular function has also been shown to be permanently altered by preadolescent undernutrition in mice (Jean-Faucher et al., 1982). Adolescent priming may also underlie population variation in ovarian function (Ellison, 1997). However, priming mechanisms involving leptin are poorly understood, although leptin has been implicated along with other hormones in priming infant immune function (Hanson et al., 2000). In addition, caloric restriction in lactating rats results in a significant reduction of circulating leptin and hypothalamic neuropeptide Y receptors (Pickavance et al., 1999), as well as in other mammals (Keisler et al., 1999).

Interpopulation variation in mean leptin levels also suggests some priming. Leptin comparisons of American and Mexican Pima populations reveal significant differences despite similar genetic heritages (Fox et al., 1999). Although leptin sexual dimorphism seems to be a common trait shared by most populations regardless of environmental conditions (Havel et al., 1996; Luke et al., 1998; Saad et al., 1997; Sheu et al., 1999), the Mapuche Indians of Chile exhibit less leptin sexual dimorphism compared to non-Mapuche Chileans (Perez-Bravo et al., 1998), perhaps due to lower adiposity and greater energetic stress in Mapuche women compared to other Chileans.

In human males, leptin and testosterone are usually inversely related due to the catabolic effects of testosterone on adipocytes (Jockenhovel et al., 1997) and increased adiposity due to greater testosterone aromatization in obese males (Bagatell et al., 1994; Stanik et al., 1981). However, Ache men exhibit significantly lower salivary testosterone levels compared to Western controls (Bribiescas, 1996, 1997) while presenting lower leptin levels. Since Ache testosterone levels are not reflective of androgen suppression of adiposity and leptin levels, other factors such as priming should be considered, since low testosterone concentrations among non-Western populations, including the Ache, are hypothesized to reflect chronic energetic stress (Bentley et al., 1993; Bribiescas, 1996, 1997; Ellison et al., 1989; Smith et al., 1975), most likely due to decreased Leydig-cell sensitivity to gonadotropin stimulation (Bribiescas, unpublished findings; Smith et al., 1975).

In the forest, gross Ache caloric intake consists of around 3,000 kcal daily (Hill et al., 1984); however, net energy availability is much less, since the Ache are extremely active, exerting much of their time either in pursuit of wild food products or in agricultural cultivation through manual agriculture (Hawkes et al., 1987; Hill et al., 1984, 1985). However, independent of caloric intake, intense physical activity has negligible effects on leptin titers in lean Western athletes, although unlike the case in Ache males, leptin is significantly correlated with fat mass (Hickey et al., 1996). The lack of correlation between leptin and somatic composition in Ache males may be an artifact of small sample size, although other investigations have demonstrated highly significant correlations in lean Western males using smaller (Hickey et al., 1996) (i.e., n = 13, $r^2 = 0.92$) or similar (Elias et al., 2000; Gippini et al., 1999; Leal-Cerro et al., 1998; Rosenbaum et al., 1997) sample sizes.

Evidence of genetic polymorphisms of leptin or its receptor has been minimal. Polymorphisms have been identified that are associated with circulating leptin levels in Mexican-Americans (Comuzzie et al., 1997), as well as with variation in proopiomelanocortin transcription (a prohormone to beta-endorphin, adrenocorticotropic hormone ACTH), which has been suggested to be a response to leptin stimulation (Hixson et al., 1999). Finally, it is unlikely that field collection methods affected leptin measurements. Laboratory comparisons of SST tube serum collection methodologies with clinical methods

utilizing standard vacutainer tubes and centrifugation showed no significant differences in male or female leptin measurements ($P < 0.01$). In addition, leptin measurements of the author using serum collected in the field at the same time as Ache samples and under identical storage and handling conditions were consistent with expected results from an American male with a fat percentage of 25% (leptin = 6.7 ng/ml).

The utility of leptin in human life history research lies in its ability to quantitatively measure a key reflection of available energy reserves. Indeed, it has been suggested that hormones are important measures of proximate mechanisms which control life history tradeoffs (Ketterson and Nolan, 1999; Stearns, 1989). However, the present results suggest that clinical descriptions of leptin physiology may reflect profiles that are unique to urban industrial populations and their well-fed, relatively sedentary lifestyle. If one were to view the Ache as well as other nonindustrialized populations as more reflective of the conditions governing most of human evolution, then one must reconsider the role of leptin in regulating human reproduction and somatic energy allocation. Although ovarian function and menarche have been suggested to be responsive to fat deposition (Frisch, 1974), leptin is a poor predictor of menarche or overall ovarian function except under the most extreme conditions (Ellison, 1982; Grinspoon et al., 1996; Matkovic et al., 1997). Indeed, ovarian function seems to be more responsive to acute changes in energy balance, far quicker than could be reflected by changes in adiposity (Bruning et al., 2000; Ellison and Lager, 1986). The lack of association between leptin and adiposity in Ache, as well as chimpanzee males, also suggests that leptin may have been a secondary hormonal regulator of energy allocation in hominid males, and that testosterone, through its anabolic action, may have played a more central role in regulating somatic energy allocation (Bribiescas, 1996, 1997, 2001; Firos and Bribiescas, unpublished findings). Future leptin investigations of non-Western populations should incorporate other endocrine factors in order to clarify associations with aging, reproductive endocrine function, sexual maturation, pregnancy, and lactation.

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