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Dehydroepiandrosterone-sulfate as a biomarker of senescence in male non-human primates

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Abstract

Numerous studies have suggested important and varying roles for dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S) in primate physiological functions. Despite these numerous claims, specific actions and significance of DHEA and DHEA-S are still equivocal. A decline of these hormones in adult humans may have functional significance, yet there is no clear relationship between functional impairments of aging and the decline in DHEA or DHEA-S levels. This current study attempts to address the natural history of adrenal hormones by presenting non-human primate evidence of the endocrinology of aging; the age-related patterns of adrenal hormone decline in three species of the subfamily Cercopithecinae, *Macaca mulatta*, *Macaca nemestrina*, and *Papio cynocephalus* are compared. It is concluded that DHEA-S and cortisol represent lineage specific markers of senescence among primates and that parallel age-related patterns of DHEA-S and cortisol likely reflect lineage specific effects, or rather, phylogenetic similarities of endocrine senescence. The use of relative adrenal hormone levels to approximate species' life expectancies is discussed.

Keywords: Dehydroepiandrosterone-sulfate; Dehydroepiandrosterone; Cortisol; Senescence; Adrenal function; *Macaca mulatta*; *Macaca nemestrina*; *Papio cynocephalus*

1. Introduction

Dehydroepiandrosterone (DHEA) and its sulfated ester, DHEA-S, circulate in the periphery of male and female primates at the highest concentrations of any adrenal hormones. Numerous publications have claimed that DHEA is an inhibitor of atherosclerosis (Barrett-Conner et al., 1986), an antiobesity steroid (Svec et al., 1994), an immunostimulate (Schurr et al., 1997; Ledochowski et al., 2001), and a neurosteroid (Flood et al., 1992; Racchi et al., 2001; Vallee et al., 2001; Ferrari et al., 2001). Despite these numerous claims, the functional significance of DHEA and DHEA-S remain unclear (Svec and Porter, 1996).

Nonetheless, DHEA and DHEA-S have been suggested as potential biomarkers of aging in human and non-human primates (Lane et al., 1997; Kemnitz et al., 2000; Roth et al., 2002). Not only is age the main determinant of DHEA and DHEA-S levels (Mobbs, 1998), but there are clear differences in DHEA and DHEA-S between young and old human and non-human primates (Orentreich et al., 1984; Short et al., 1989; Kemnitz et al., 2000; Goncharova and Lapin, 2002). Circulating DHEA and DHEA-S levels have been shown to consistently decrease from juvenile to late adulthood in a variety of primate species including crab-eating macaques (Meusy-Dessole and Dang 1985), sooty mangabeys (Mann et al., 1983), rhesus macaques (Koritnik et al., 1983; Goncharova and Lapin, 1999; Herndon et al., 1999; Kemnitz et al., 2000; Goncharova and Lapin, 2002), and free-ranging yellow baboons (Sapolsky et al., 1993). In addition, Copeland and others (1985) noted that DHEA-S levels were lower in older compared to younger male and female chimpanzees.

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Although the cellular basis for the decline in DHEA and DHEA-S is not currently known (Mobbs, 1998) and the roles of DHEA and DHEA-S in maintaining organismal function are still speculative (Svec and Porter, 1998), it is clear that DHEA and DHEA-S levels decline with age in primates, with the highest levels being in the neonatal period with the exceptions of humans and chimpanzees which demonstrate highest levels just before pubertal onset (Culter et al., 1978; Copeland et al., 1985; Orentreich et al., 1992). Because DHEA and DHEA-S levels behave in such a consistent manner, they may be used as crude estimates of maximum lifespan within species of the Primate order.

Comparison of closely related species provides an opportunity to investigate the relationship of DHEA and DHEA-S to life history traits among primates. If DHEA and DHEA-S represent lineage specific markers of senescence among primates, then one might expect DHEA and DHEA-S levels to asymptotically approach zero as the organism approaches its age of peak mortality due to senescence. Furthermore, the more closely related the species, the more similarities in age-related patterns of DHEA and DHEA-S levels are likely to reflect lineage specific effects, or rather, phylogenetic similarities of endocrine senescence. Consequently, we compared the age-related pattern of DHEA and DHEA-S decline in three species of the subfamily Cercopithecinae, *Macaca mulatta*, *Macaca nemestrina*, and *Papio cynocephalus* sp. We included cortisol in our analyses as a third measure of adrenal function.

We hypothesize that: (1) cortisol, DHEA and DHEA-S levels will progressively decline with increasing age in samples of captive male rhesus macaques, pig-tailed macaques, and savanna baboons; (2) the patterns of decline of adrenal hormones will be similar for these three species and the patterns of decline will be more similar between the two macaque species due to increased phylogenetic relatedness; and (3) the age at which average adrenal hormone levels asymptotically approach zero will approximate the average reported life spans for captive macaques and baboons.

2. Materials and methods

This cross-sectional survey utilizes 69 male rhesus macaques (*M. mulatta*) of Indian origin between 3 and 14 years of age and 43 male pig-tailed macaques (*M. nemestrina*) between 3 and 12 years of age maintained at the Tulane National Primate Research Center, Covington, LA, USA. Animals were housed in one-half and one-quarter acre corrals as well as smaller outdoor enclosures and individual restraining cages. Of the 43 pig-tailed macaques used, 35 were housed in outdoor corrals (0.0003–0.0006 animals/m^2), 7 in individual cages (0.022 animals/m^2), and one in a small outdoor enclosure (0.006 animals/m^2). Of the 69 rhesus macaques, 49 were housed in outdoor corrals (0.0007–0.008 animals/m^2), 14 in individual cages (0.233 animals/m^2), and 6 in small outdoor enclosures (0.04–0.08 animals/m^2). These values are reported for accurate representation of data. There was no effect of cage size on any of the variables of interest and they were not included in further analyses. In general, the corrals demonstrate a consistent and seminatural ecological context (Sade, 1964). All measurements took place between October 1998 and January 1999, the rhesus' common breeding season.

Additionally, 21 hybrid male baboons between 1.7 and 13.2 years of age were sampled. These animals represent all males over 1.7 years of age in a hybrid breeding colony of approximately 330 savanna baboons (sex ratio of males to females, 1:12) of both Olive (*Papio cynocephalus anubis*) and Yellow (*Papio cynocephalus cynocephalus*) phylogenetic heritage. All animals were housed in a single one-acre outdoor corral, a semi-natural ecological context that accommodates normal physical and social activity (Coelho, 1985). Baboon measurements took place during the population's biannual health inspection in early December 1999.

All animals were provisioned with Purina Monkey Chow (Ralston Purina Co., St Louis, MO) daily. Diet was supplemented with fresh fruit weekly and water was available ad libitum. Matrilineal data and precise chronological ages were maintained in the Center's computer system. In order to minimize inter-observational error, morphometric measurements were made by one investigator (MPM) when possible. However, a small number ($<10\%$) were made by another trained investigator (MAM).

All animals were anesthetized with ketamine hydrochloride (10 mg/kg), a widely accepted dissociative anesthetic which has been demonstrated to have no significant effects on serum hormone levels or production rates (Zaidi et al., 1982). Each animal was examined once, between 0800 and 1030 hours to minimize any circadian effect. Body weight, length from the occipital node to the ischeal callosity, upper arm circumference, tricep, abdominal, and subscapular skinfolds were recorded as described earlier (Muehlenbein et al., 2001; Muehlenbein et al., 2002).

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). The sera from the blood was stored at -40 °C until assayed for DHEA, DHEA-S, and cortisol using solid-phase ^{125}I radioimunoassay procedures (DHEAS: Diagnostic Products Corp., LA; DHEA and cortisol: Diagnostic Systems Laboratory, Texas). Intra-assay coefficients of variation were less than 5.9% for all assays.

Using Statistical Package for the Social Sciences, version 10.0 for Macintosh, Analysis of Covariance (ANCOVA) was employed to determine any age by species interactions; this interaction being indicative of differential rates of

Table 1
Age distribution of macaque and baboon samples

Macaque age groups[a]	Rhesus, $N = 69$	Pig-tailed, $N = 43$
Ages 3.5–5.0 (adolescents)	17	22
Ages 5.1–8.9 (sub-adults)	27	10
Ages 9.0–15.0 (prime-adults)	25	11
Baboon age groups[b]	$N = 20$	
Ages 2.0–3.9 (testes not yet dropped)	6	
Ages 4.0–5.9 (growth spurt)	4	
Ages 6.0–9.9 (young adulthood)	5	
Ages 10.0–14.9 (prime adulthood)	5	

[a] Muehlenbein et al. (2002).
[b] Coelho (1985) and Castracane et al. (1986).

change between the species in the variable under question. For each ANCOVA, a mass index (Primate Mass Index (PMI) = weight (kg) divided by crown-rump length squared (m^2)) was fixed in the model to control for body size differences and any influence such differences would have on relative adrenal hormone levels and their changes throughout time. Bivariate associations between the hormonal and morphometric factors were assessed using Pearson's Correlation Coefficients as well as the nonparametric correlation coefficients Spearman's rho and Kendall's tau. For all statistical tests, alpha was set at $p < 0.05$.

3. Results

3.1. Average values

Table 1 shows the age distribution among the three species sampled here. Comparison with other studies (Schwartz and Kemnitz, 1992; Bercovitch, 1989) suggests that the macaques and baboons in this study are comparable in terms of morphometric measures to other populations.

Table 2 shows the average values (±SEM) for the adrenal hormones of the rhesus ($N = 69$), pig-tailed ($N = 43$), and baboon ($N = 21$) samples. The three species differed significantly from one another in DHEA, DHEA-S, and cortisol levels. The pig-tailed sample had a significantly higher DHEA level, followed by the rhesus and baboon samples. The rhesus sample had a significantly higher DHEA-S level, followed by the baboons and pig-tailed samples. For cortisol, the baboon sample had the highest values, followed by the pig-tailed and rhesus samples. Furthermore, the sample of rhesus was slightly older. However, controlling for this age difference between the three samples did not impact any of the significant differences.

3.2. Impact of seasonality

As discussed above, macaque measurements were collected over the course of the beginning to the middle of the rhesus breeding season. Changes in adrenal hormone levels related to the breeding season could have confounded differences between the two macaque species and/or their relationship with morphometric variables within the rhesus. Therefore, partial correlations between the hormones and time of data collection (dates collapsed into week intervals; weeks 1–8 for the rhesus and 9–12 for the pig-tailed) among the macaque species were employed while controlling for age. Among the rhesus, there is a negative correlation of week with DHEA ($r = -0.2361$; $p = 0.053$), but not with DHEA-S or cortisol. We attribute the negative associations of these measures with week of sampling to two facts: (1) larger males were sampled first, thereby potentially biasing the findings of higher hormone levels in the early weeks of data collection; (2) variation in hormone levels over the breeding season.

In contrast, among the pig-tailed sample there is a significant positive correlation of week with DHEA-S ($r = 0.5674$; $p = 0.000$), DHEA ($r = 0.3504$; $p = 0.023$), and cortisol ($r = 0.3973; 0.009$). We attribute the positive association of these measures with week of sampling to the fact that smaller pig-tailed males were sampled first. In order to control for the confounding effects of sampling, week of data collection was included as a control in subsequent analyses of the relationship between age and hormonal measures. Thus the relationships between age and hormonal measures shown in Table 3 represent partial correlations controlling for week of data collection.

Table 2
Average values (±SEM; all ages combined) for adrenal hormones

Variable	Rhesus, $N = 69$	Pig-tailed, $N = 43$	Baboon[a], $N = 20$	p-Value[b]
Age (years)	8.12 ± 0.44	6.61 ± 0.42	6.48 ± 0.83	ns
DHEA (ng/ml)	21.61 ± 0.89	30.46 ± 0.81	15.59 ± 1.45	0.000[c]
DHEA-S (μg/dl)	17.81 ± 1.39	7.57 ± 0.85	11.93 ± 3.00	0.000[c]
Cortisol (μg/dl)	37.80 ± 1.58	44.72 ± 1.75	48.34 ± 2.98	0.022[c]

[a] One DHEA-S value of 51.97 μg/dl was considered an outlier and removed from the analyses, resulting in $N = 20$.
[b] Overall significant difference between groups assessed using ANCOVA controlling for age.
[c] Significant difference ($p < 0.05$) between all three species.

Table 3
Correlations (Pearson correlation coefficients for macaques, Spearman correlation coefficients for baboons (controlling for week of data collection)) of hormonal variables with age

Variable	Rhesus, $N = 69$	Pig-tailed, $N = 43$	Baboon, $N = 21$
Cortisol (μg/dl)	−0.4235**	−0.3536*	−0.4836*
DHEA (ng/ml)	−0.2225	0.0972	−0.3167
DHEA-S (μg/dl)	−0.3229**	−0.4870**	−0.6762**

DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone-sulfate. *$p < 0.05$; **$p < 0.01$.

3.3. Age patterns of adrenal hormone levels

The relationships between hormonal measures and age are shown in the correlation matrix contained in Table 2. For all three species, cortisol and DHEA-S were negatively correlated (zero-order) with age.

For all three species there were large variations in hormone levels, making any evident trends throughout development difficult to visualize. ANCOVA procedures were used to determine significant age by species interaction for these adrenal hormones while controlling for PMI. For DHEA-S and cortisol there were no age by species interaction, indicating an approximately parallel decline in these values for all three species. For DHEA, baboons and rhesus had similarly declining values whereas the pig-tailed sample actually showed a non-significant increase with age.

Fig. 1 presents three scatterplots of adrenal hormones by age for the rhesus macaque sample. There was no significant decrease in DHEA levels throughout the rhesus sample ($r^2 = 0.0492$; $p = 0.067$). However, both DHEA-S ($r^2 = 0.1030$; $p = 0.0072$) and cortisol ($r^2 = 0.1791$; $p = 0.0003$) levels decreased with age. Fig. 2 presents three scatterplots of adrenal hormones by age for the pig-tailed macaque sample. For neither DHEA ($r^2 = 0.0819$; $p = 0.06$), DHEA-S ($r^2 = 0.0425$; $p = 0.18$), nor cortisol

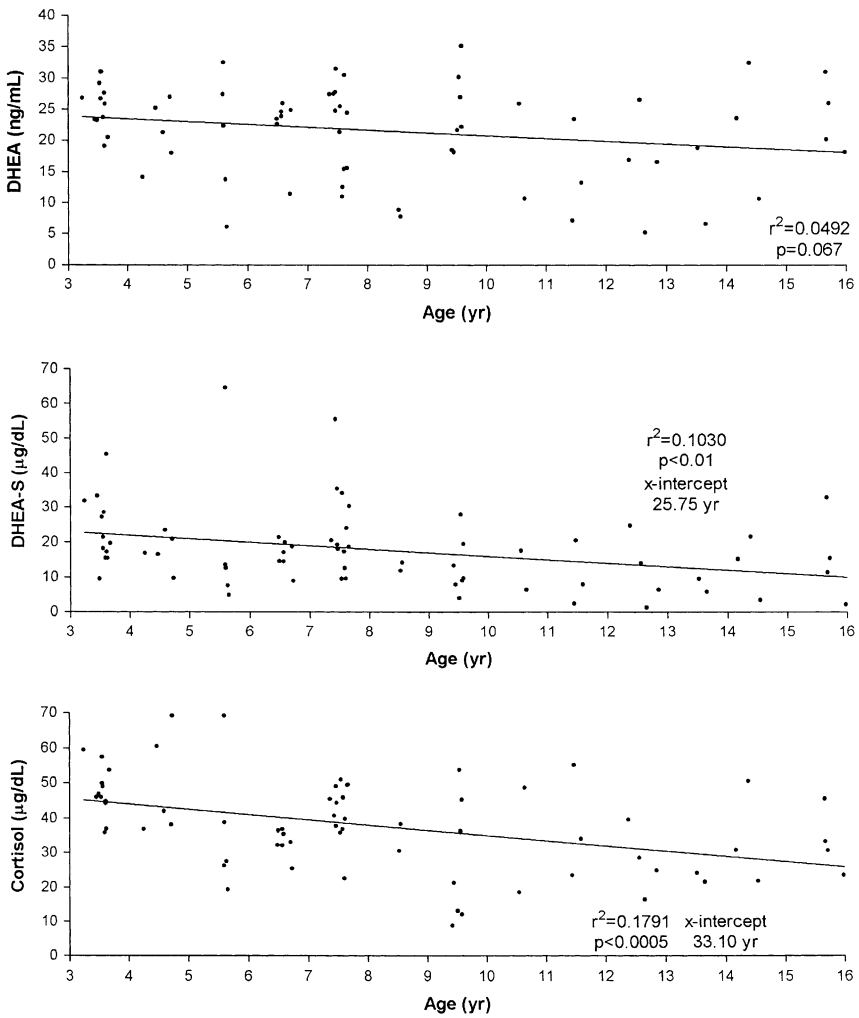

Fig. 1. Age-related changes in adrenal hormones in the rhesus macaque sample ($N = 69$). There was no significant decrease in DHEA levels throughout the rhesus sample ($r^2 = 0.0332$; $p = 0.12$). However, both DHEA-S ($r^2 = 0.1344$; $p < 0.005$) and cortisol ($r^2 = 0.1607$; $p < 0.005$) levels decreased with age. Extrapolating the linear trends in DHEA-S and cortisol revealed x-intercepts at 21.98 and 34.29 years of age, respectfully.

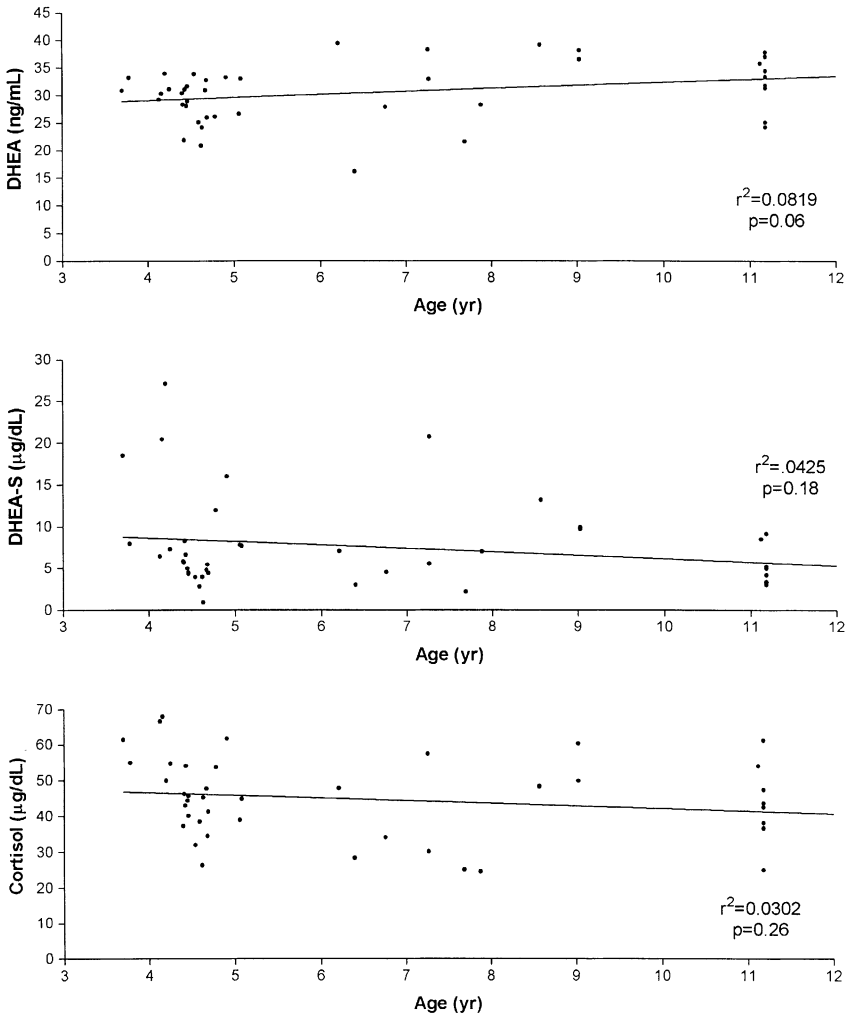

Fig. 2. Age-related changes in adrenal hormones in the pig-tailed macaque sample ($N = 43$). For neither DHEA ($r^2 = 0.0819$; $p = 0.06$), DHEA-S ($r^2 = 0.0425$; $p = 0.18$), nor cortisol ($r^2 = 0.0302$; $p = 0.26$) was there a significant decrease with age in the pig-tailed macaque sample.

($r^2 = 0.0302$; $p = 0.26$) was there a significant decrease with age. Fig. 3 presents three scatterplots of adrenal hormones by age for the baboon sample. There was no significant decrease in DHEA levels throughout the baboon sample ($r^2 = 0.0919$; $p = 0.19$). However, both DHEA-S ($r^2 = 0.5522$; $p < 0.0005$) and cortisol ($r^2 = 0.2855$; $p < 0.05$) levels decreased with age.

In an attempt to use age-related profiles of DHEA, DHEA-S, and cortisol to approximate average life expectancy, we extrapolated the linear trends in hormones to zero for all three species. The point at which the hormone level asymptotically approached zero on the x-axis was determined using GLM to estimate 95% mean prediction level. For the rhesus, extrapolating the linear trends in DHEA-S and cortisol revealed x-intercepts at 25.75 and 33.10 years of age, respectfully. These results are similar to the maximum reported lifespan of wild (25–35 years) and captive (17.6–25 years) rhesus macaques (Tigges et al., 1988; Turnquist and Kessler, 1989; VanWagenen, 1972; Napier and Napier, 1985; Bowden and Jones, 1979).

For the pig-tailed, extrapolating the linear trend in DHEA-S revealed an x-intercept at 24.84 years of age, which is very close to the average reported lifespan of wild pig-tailed macaques (26.3 years) (Napier and Napier, 1985). For the baboons, the x-intercepts were 11.73 and 29.75 years of age for DHEA-S and cortisol, respectfully. The average reported lifespan of baboons ranges from 30 to 45 years (Rowell, 1966; Napier and Napier, 1985; Lapin et al., 1979).

4. Discussion

The results obtained here present two interesting points of consideration. First, DHEA-S and cortisol levels may predict average reported life expectancy in samples of captive male rhesus macaques and baboons. Second, DHEA values were much more variable for all three species than were DHEA-S values, leading to less significant linear regression fits for DHEA and even a slight non-significant trend towards higher DHEA values in older pig-tailed

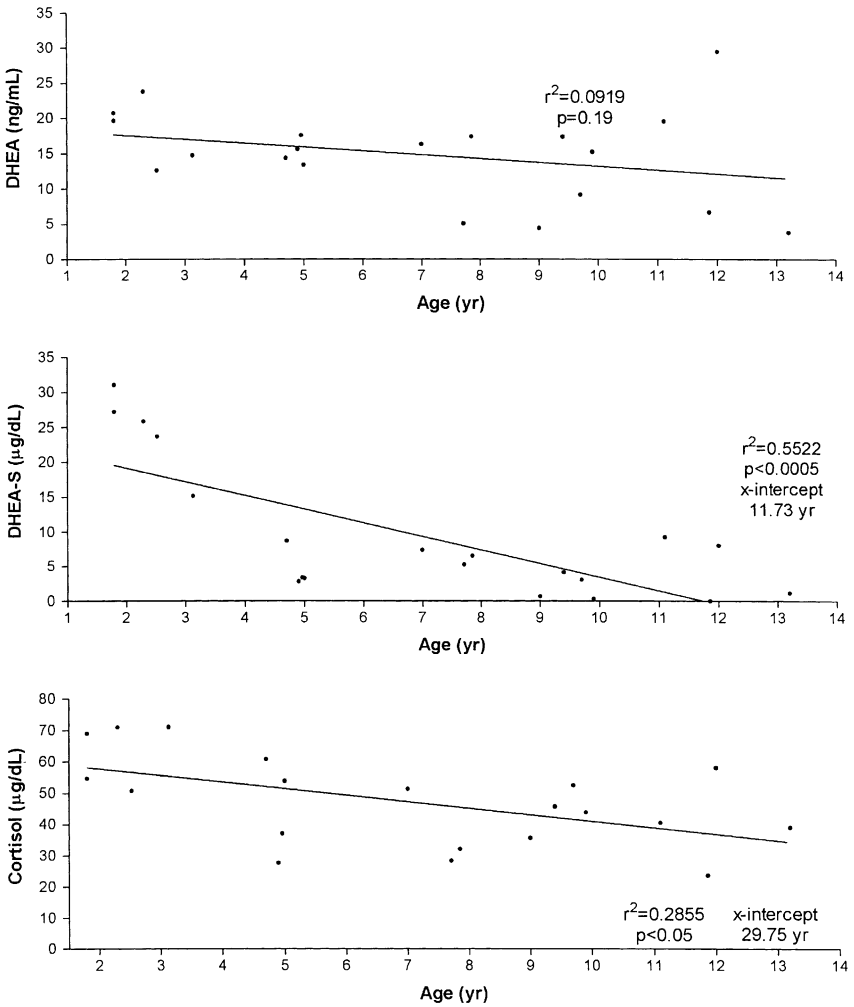

Fig. 3. Age-related changes in adrenal hormones in the baboon sample ($N = 20$). There was no significant decrease in DHEA levels throughout the baboon sample ($r^2 = 0.0919$; $p = 0.19$). However, both DHEA-S ($r^2 = 0.5522$; $p < 0.0005$) and cortisol ($r^2 = 0.2855$; $p < 0.05$) levels decreased with age. Extrapolating the linear trends in DHEA-S and cortisol revealed x-intercepts at 11.73 and 29.75 years of age, respectfully.

macaques. It is interesting to note that nearly all studies that attempt to investigate age-related changes in human and non-human primate adrenal function rarely measure changes in both DHEA and DHEA-S, but rather, usually only measure one or the other.

4.1. Lifespan approximation

Because adrenal hormones behave in such a consistent way throughout mammalian lifecycles, they may be used as crude estimators of maximum lifespan within species of the Primate order. Martin and others (1977) have suggested the use of single-sample, serum testosterone levels as potentially determinant of age in adolescent male chimpanzees. Here we have tried to address the use of adrenal hormone levels as potentially determinant of age and reported life expectancy in captive male macaques and baboons. We hypothesized that the age at which average adrenal hormone levels asymptotically approached zero would approximate the average reported lifespans for captive male macaques and baboons.

According to literature reporting maximum lifespan of the non-human primate species used here (Rowell, 1966; VanWagenen, 1972; Bowden and Jones, 1979; Lapin et al., 1979; Napier and Napier, 1985; Tigges et al., 1988; Turnquist and Kessler, 1989), adrenal hormone levels should asymptotically approach zero around 25 years of age for the two macaque samples, and around 30–35 years for the baboon sample. To test this hypothesis, linear regression was used to approximate average life expectancy based on adrenal hormone values for all three species. DHEA, DHEA-S, and cortisol values were plotted for each species on scatterplots of hormone vs. age, with a best-fit linear regression line (GLM to estimate 95% mean prediction level) extrapolated to the zero value for the hormone under investigation.

Extrapolating the linear trend in rhesus macaque DHEA-S and cortisol values (Fig. 1) indicated a DHEA-S value of

zero at 25.75 years of age, and a cortisol value of zero at 33.10 years of age, both figures coincide with the range of maximum reported rhesus macaque lifespan. For the pig-tailed sample (Fig. 2), extrapolating the DHEA-S values indicated a value of zero at 24.84 years, which coincides with estimates of average pig-tailed macaque lifespan. Neither DHEA nor cortisol were able to accurately predict average reported lifespan for pig-tailed macaques. For the baboon sample (Fig. 3), DHEA-S dropped to zero at 11.73 years of age, which is much too young to be considered an accurate predictor of lifespan by any means. However, cortisol dropped to zero at 29.75 years of age for the baboon sample, which coincides with other estimates of average baboon lifespan. These results suggest that, all things being equal, DHEA-S and cortisol levels may predict average reported life expectancy in samples of captive male rhesus macaques and baboons.

Qualitatively, these age-related changes in adrenal function mirror what is found in humans: adrenal hormone levels are highest in young adults and fall progressively until at the end of life the values asymptotically approach zero (Svec and Porter, 1996). DHEA-S levels decline by almost one-quarter every decade after forty years of age in humans (Belanger et al., 1994). The age-related decline in DHEA-S levels in male and female rhesus macaques is approximately twice the rate of decline observed in humans (Lane et al., 1997). Interestingly, average male human lifespan is approximately twice that of male macaques.

4.2. Lineage specific changes in adrenal function

Of all placental mammals investigated, only human and non-human primates have relatively high circulating levels of DHEA and DHEA-S (Svec and Porter, 1996). Many investigators have found that circulating DHEA and DHEA-S levels consistently decrease with increasing age in humans, macaques, and baboons alike (Koritnik et al., 1983; Sapolsky et al., 1993; Kemnitz et al., 2000; Roth et al., 2002; Goncharova and Lapin, 2002). For example, DHEA and DHEA-S declined significantly with age in a sample of 134 captive baboons (Castracane et al., 1981). Likewise, DHEA-S was lower in 6–36 month old female rhesus macaques compared to younger age groups (Cutler et al., 1978). Among humans, DHEA-S levels decline by almost one-quarter every decade after forty years of age (Belanger et al., 1994). In a longitudinal study involving 97 normal, healthy men, DHEA-S declined in 67% of subjects (Orentreich et al., 1992). Furthermore, decreasing serum DHEA levels seem to parallel the age-associated decrements in many physiologic processes (Weksler, 1993; Svec and Porter, 1996; Ledochowski et al., 2001).

We have previously reported that male rhesus macaques demonstrated significantly higher DHEA-S levels than pig-tailed macaques (18.0 ± 11.7 vs. 7.6 ± 5.4 μg/dl) when controlling for age (Muehlenbein et al., 2002). Furthermore, DHEA-S levels declined from the youngest age group for both species (Muehlenbein et al., 2002). We have also previously reported that DHEA-S progressively declined from infancy through young adulthood in baboons (Muehlenbein et al., 2001). In this current study we demonstrate that the three species differed significantly in DHEA, DHEA-S, and cortisol levels from one another (Table 2). The pig-tailed sample had the highest DHEA level; the rhesus sample had the highest DHEA-S level; and the baboon sample had the highest cortisol level. Significantly different levels of adrenal hormones between the three species does seem to suggest some difference in adrenal function. Whether these differences are related to the relative size of the adrenal gland, its responsiveness to stimulation, the relative production of these hormones, or some combination of these factors in the three species remains unclear (Deslypere et al., 1985).

Smail et al. (1982) have demonstrated that, in a mixed sex sample of 76 rhesus macaques ages 3 months to 5 years, DHEA-S declined significantly with age, but DHEA or cortisol did not. In the present study, DHEA-S and cortisol were significantly (negatively) correlated with age (Table 3) in all three species. On the other hand, DHEA levels were much more variable in all three species and thus, were not significantly correlated with age. Besides the fact that adrenal hormones correlate with age, the claim that DHEA is a biomarker of aging in primates is further evidenced by the numerous publications that demonstrate age as being the main determinant of DHEA and DHEA-S levels (Lane et al., 1997; Mobbs, 1998). Results of this current study indicate that for the baboon sample DHEA-S was a significant predictor of age. In the rhesus sample, cortisol was the only variable to enter the model (predicting age). Similarly, DHEA-S was the only variable to enter the pig-tailed model. This is in contrast with Smail et al. (1982) who found that neither DHEA or DHEA-S significantly predicted age in a mixed sex sample of pig-tailed macaques ages 6 months to 9 years.

For all three species there were large variations in adrenal hormone levels, making any evident trends throughout development difficult to visualize. But despite substantial species differences in cortisol and DHEA-S levels, these variables show little difference in age-related patterns between the species: DHEA-S and cortisol levels seem to follow a significant linear decrease in the rhesus and baboon samples (non-significant trend in the pig-tailed sample). Furthermore, there were no age by species interaction for DHEA-S and cortisol levels (ANCOVA controlling for PMI), indicating an approximately parallel decline in these values for all three species. Interestingly, the decline in adrenal hormone levels was no more parallel in the two macaque species than it was between the rhesus and baboons. This may be because adrenal hormone levels were too variable in the pig-tailed sample, as further evidenced by the lack of association between age and DHEA for the pig-tailed.

Within this sample of non-human primates, DHEA levels were highly variable and thus, were not significantly correlated with age. Why DHEA-S and cortisol values might change more predictably with age than DHEA cannot easily be explained here. However, such results may be indicative of changes in the zona reticularis (ZR) with age. That is, although the cellular basis for adrenal senescence is not definitively known (Mobbs, 1998), it has been suggested that the ZR of the adrenal gland changes with age (Parker et al., 1981; Roberts, 1999), with a decrease in ZR cell number via apoptosis and a loss of proliferative capacity of the adrenocortical cells (Hornsby, 1995, 2002). Unlike DHEA-S which is produced in large concentrations by the ZR of the adrenal gland, DHEA is produced in much lower concentrations by the ZR and is synthesized by other tissues of the body, including the gonads (Hornsby, 1995). Thus, cellular changes in the adrenal gland may explain why DHEA-S and cortisol are more significantly correlated with aging than is DHEA, whose concentration does not rely solely on production by the senescing adrenals.

In brief, the results obtained here support the understanding that DHEA-S and cortisol levels decline with age in non-human primates. Furthermore, the age-related changes in DHEA-S and cortisol were similar in these three species of Cercopithecines (Family Cercopithecinae, Old World Monkeys). We therefore suggest that these conservative changes in adrenal function or rather, 'adrenal senescence,' represent a lineage specific effect, or 'a feature characteristic of a lineage that does not vary within that lineage and differs from others;' lineages being groups of species related by shared ancestry (Stearns, 1992, p. 222). The more closely related the species, the more similarities in age-related patterns of DHEA-S and cortisol levels are likely to reflect lineage specific effects, or rather, phylogenetic similarities of endocrine senescence. To confirm this would require two further lines of future research: (1) sampling more diverse Cercopithecines to confirm similar trends and (2) sampling other lineages, such as the subfamily Colobinae, to determine lineage specificity.

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