



Published in final edited form as:

Am J Phys Anthropol. 2013 August ; 151(4): 643–648. doi:10.1002/ajpa.22300.

Brief Communication: Adrenal Androgens and Aging: Female Chimpanzees (*Pan troglodytes*) Compared With Women

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Abstract

Ovarian cycling continues to similar ages in women and chimpanzees yet our nearest living cousins become decrepit during their fertile years and rarely outlive them. Given the importance of estrogen in maintaining physiological systems aside from fertility, similar ovarian aging in humans and chimpanzees combined with somatic aging differences indicates an important role for nonovarian estrogen. Consistent with this framework, researchers have nominated the adrenal androgen dehydroepiandrosterone (*DHEA*) and its sulfate (*DHEAS*), which can be peripherally converted to estrogen, as a biomarker of aging in humans and other primates. Faster decline in production of this steroid with age in chimpanzees could help explain somatic aging differences. Here, we report circulating levels of *DHEAS* in captive female chimpanzees and compare them with published levels in women. Instead of faster, the decline is slower in chimpanzees, but from a much lower peak. Levels reported for other great apes are lower still. These results point away from slowed decline but toward increased *DHEAS* production as one of the mechanisms underlying the evolution of human longevity.

Keywords

dehydroepiandrosterone sulfate; senescence; aging rates; human longevity

Humans have remarkably long lives compared to other members of the great ape clade (Raisz, 1999; Robson et al., 2006). Survival well beyond menopause is a distinctive feature of human life history (Bogin and Smith, 1996) and contrasts with patterns observed in most other mammals including all nonhuman primates (Levitis and Lackey, 2011). Because human life expectancies have nearly doubled in some populations since the nineteenth century (Oeppen and Vaupel, 2002), the human pattern is widely assumed to be a novelty of recent history. But those recent changes are largely due to reductions in infant and juvenile mortality (Oeppen and Vaupel, 2002). Where nutritional and technological advances responsible for the reduced old age mortality of some contemporary populations (Kirkwood,

2008; Hawkes, 2010) are absent, women have continued to be economically productive well beyond the fertile ages (Hamilton, 1966; Hawkes et al., 1989, 1997; Kaplan et al., 2000; Blurton Jones et al., 2002; Kaplan et al., 2010) and in hunter-gatherer socioecologies they show little decline in strength into their sixties (Blurton Jones and Marlowe, 2002; Walker and Hill, 2003).

Hypotheses about why natural selection favored slower aging in many human somatic systems (Hawkes et al., 1998; Kaplan et al., 2000; Hawkes, 2003; Kaplan et al., 2010) are silent on the physiological mechanisms that make it possible. This mechanism question is especially pressing because, aside from fertility, the steroid hormones collectively referred to as estrogen affect diverse tissues and cells (osteal: Raisz, 1999; cardiovascular: Kim and Levin, 2006; Turgeon et al., 2006; immunological: Wise et al., 2009; neurological: Lacreuse, 2006; Wise et al., 2005). While men produce testosterone, which is locally converted to estrogen in peripheral tissues throughout life, women produce ovarian estrogen only as ovarian follicles grow from a nonrenewing stock that begins declining before birth (Peters et al., 1978; McGee and Hseuth, 2000).

When follicle stocks fall below a threshold needed to support ovulation, cycling stops (Faddy and Gosden, 1996; McGee and Hsueh, 2000) and, estrogen secretion plummets to levels so low that it remains controversial whether postmenopausal ovaries produce any (Labrie et al., 2011). Many aspects of somatic aging in Western women have been linked with this drop (e.g., Riggs et al., 1998; Pfeilschifter et al., 1978; Turgeon et al., 2006; Stevenson and Thornton, 2007; Wise et al., 2009; Gibbs, 2010; Henn, 2010). Yet postmenopausal declines in physiological competence are not large enough to cause an inflection in mortality (Hamilton, 1966; Gavrilov and Gavrilova, 1991) or stop postmenopausal women from continuing high levels of economic productivity (e.g., Hawkes et al., 1989, 1997). If estrogen is important for physiological maintenance, postmenopausal women must produce it from nonovarian sources. Other steroids that can be converted to estrogen in peripheral tissues are obvious candidates.

After cholesterol, the adrenal androgen dehydroepiandrosterone (*DHEA*) and its sulfate ester dehydroepiandrosterone sulfate (*DHEAS*) are the most abundant steroids circulating in young human adults. They are the main products of the human adrenal gland (Longcope, 1986), circulating at nanomolar and micromolar concentrations respectively (Longcope, 1995; Baulieu, 1996; Longcope, 1996). Peripherally, *DHEA* and *DHEAS* are interconverted by sulfotransferase enzymes present in a wide variety of tissues (Fujikawa et al., 1997; Dalla Valle et al., 2006). As *DHEAS* has a longer circulating half-life and concentration several orders of magnitude higher, it is generally considered to be a reservoir for *DHEA* (Longcope, 1986; Rosenfeld et al., 1975; but see Hammer et al., 2005; Siiteri, 2005 for debate). Circulating levels are “1,000 to 10,000 times higher than those of estradiol” in women (Labrie et al., 1998:322), so that intracrine conversion of *DHEA* in peripheral target tissues may be responsible for “75% of estrogen before menopause and close to 100% after menopause” (Labrie, 1991:C116).

Faster decline in adrenal androgen production across adulthood might help explain why chimpanzees become decrepit while their ovaries are still secreting estrogen. Follicle stocks

decline with age at the same rate in chimpanzees and humans (Jones et al., 2007); and, like us, they can have last pregnancies into their forties (Roof et al., 2005; Emery Thompson et al., 2007). But chimpanzees display geriatric symptoms in their thirties (Goodall, 1986; Huffman, 1990; Nishida et al., 2003; Matsuzawa, 2007). Even in captivity where mortality is reduced (Dyke et al., 1995; Hill et al., 2001), chimpanzees rarely live beyond their cycling years (Lacreuse et al., 2008; Herndon et al., 2012).

Declines in circulating levels of *DHEAS* have been measured in several primate species; and those declines have been proposed as biomarkers of aging in humans and nonhuman primates (Lane et al., 1997; Kemnitz et al., 2000; Roth et al., 2002). Ingram et al. (2001:1030–1) say that

“The rate of age-related change in a candidate biomarker should be proportional to differences in lifespan among related species. For example, the rate of change in a candidate biomarker of aging in chimpanzees should be twice that of humans (60 vs. 120 years maximum lifespan); in rhesus monkeys about three times that of humans (40 vs. 120 years maximum lifespan).”

This expectation is consistent with general scaling assumptions and supported empirically for circulating *DHEAS* data on captive rhesus and humans (Lane et al., 1997). Building on these observations we hypothesized that circulating levels of *DHEAS* would decline twice as fast with age in female chimpanzees when compared to published levels in women.

MATERIALS AND METHODS

To test this hypothesis, we requested blood samples from female chimpanzees at Yerkes National Primate Research Center. Samples were drawn only when subjects were sedated for reasons unrelated to this project with a protocol approved by IACUCs at the University of Utah and Yerkes. During 2007, 2009, 2010, and 2011, samples were taken from 70 females then immediately processed for serum and kept frozen until analyzed for *DHEAS* by the Biomarkers Core Lab at Yerkes using RIA for samples from 2007 and LC-MS thereafter (Supporting Information Table S1). Here, we compare the results from 65 chimpanzee females over the age of 15 with a combined sample of published *DHEAS* levels for 71 Czech women between the ages of 20 and 80 reported by Sulcova et al. (1997), 68 Italian women between the ages of 19 and 78 reported by Ravaglia et al. (1996), and 530 Australian women aged 20–76 reported by Davison et al. (2005) (see Supporting Information Table S2). We used these sources because their published figures allowed recovery of individual *DHEAS* levels, not just age class means and because they provided *DHEAS* levels across adulthood.

Some of our chimpanzee measurements came from subjects on hormonal contraception (Supporting Information Table S1). As exogenous hormone supplements reduce *DHEAS* levels 26–32% in women (White et al., 2005), we looked for a similar effect in chimpanzees by splitting our sample into the 53 measurements taken when a subject was not on hormone contraception and the 12 when on. Comparison of models fitted to these subsamples (Supporting Information Fig. S1) showed no substantial differences.

Methods differed slightly among the human studies, so we used R statistical package (R Development Core R Development Core Team, 2011) to fit models of *DHEAS* concentrations against age for each dataset separately (Supporting Information Fig. S2) and found that the 95% confidence intervals overlap. To evaluate representativeness of our sample for women, we extracted 5-year age class means of *DHEAS* levels from figures reported by Orentreich et al. (1984), fit a model using the procedure described above, and found very close agreement between models of human *DHEAS* decline in our combined human sample and that of Orentreich and colleagues (Table 1).

We then compared our combined human sample to our chimpanzee sample by fitting a number of functional forms, both linear and nonlinear, with maximum likelihood estimation in order to approximate the relationship between *DHEAS* concentrations and age. Using Akaike Information Criterion (Akaike, 1974) we determined the best fitting models for each species.

RESULTS

A logarithmic function where $DHEAS (\mu\text{g/dL}) = 189.73 - 33.86 \times \ln(\text{age})$ best fit the chimpanzee data, while an exponential model where $DHEAS (\mu\text{g/dL}) = e^{(6.24 - 0.03 \times \text{age})}$ fit the human data best (Table 1). Using these models, we estimated peak concentrations of *DHEAS* at the start of adulthood (using 15-years-old for chimpanzees and 20 years for humans because these are close to the beginning of adulthood in each species and allow comparison of 5-year age class means; Table 1) and average rates of *DHEAS* decline across 5-year age classes (Table 2). We calculated the ratio of chimpanzee to human slope for each 5-year age class after peak in Table 2 to simplify comparison. Figure 1 shows the distribution of individual *DHEAS* concentrations by age and species, with the best-fit models for each.

Contrary to the hypothesis that circulating levels of *DHEAS* would decline twice as fast in chimpanzees as they do in humans, declines are more gradual in chimpanzees. Average declines in chimpanzee *DHEAS* range between 21 and 25% of human rates (Table 2). Compared to chimpanzees, women begin adulthood with more than three times the circulating levels of *DHEAS* (281.46 vs. 89.04 $\mu\text{g/dL}$ for chimpanzee females; Table 1). Human concentrations do not fall to the highest chimpanzee levels until the tenth 5-year interval—starting at 65 and ending at 69.

DISCUSSION

Circulating levels of *DHEAS* in our chimpanzee sample do not support the hypothesis of a faster decline with age. Instead, when compared to women, female chimpanzees begin adulthood with *DHEAS* concentrations less than one-third as high that decrease at less than one fourth the rate. Assuming that *DHEAS* levels are an index of investment in somatic maintenance, we should have anticipated that maximum circulating levels would be substantially higher in humans. Evolutionary theories of aging link slower senescence and longer average adult life spans to increased somatic investment (Williams, 1957; Hamilton, 1966; Williams, 1966; Kirkwood and Rose, 1991). More investment in maintenance reduces

vulnerability to mortality (e.g., Ricklefs, 1998), and selection favors more maintenance when that tradeoff increases lifetime fitness (Hamilton, 1966; Williams, 1966; Kirkwood and Rose, 1991; Hawkes, 2003).

The chimpanzee-human *DHEAS* comparison is consistent with the inference that adrenal steroids play an important role in somatic maintenance. In humans—and we assume in chimpanzees as well—estrogenic bioactivity is important for both fertility and somatic maintenance. This link between higher *DHEA/S* levels and increased somatic maintenance in humans is consistent with a broader hypothesis that higher circulating levels of *DHEAS* in primates versus nonprimate mammals (Labrie et al., 2001; Nguyen and Conley, 2008) contribute to greater longevity in our order (e.g., Austad and Fischer, 1992; Charnov and Berrigan, 1993). But this generalization warrants further scrutiny in light of complex variation in adrenal glands across the order (Conley et al., 2004; Nguyen and Conley, 2008). An implicit corollary of the hypothesis that *DHEAS* plays a role in primate longevity is that similarities in somatic maintenance between chimpanzees and other great apes derive partly from similarities in *DHEAS* levels. Bernstein and collaborators (Bernstein et al., 2012) recently presented data inconsistent with this corollary.

They reported serum levels of *DHEA* and *DHEAS* across the life span in captive great apes and showed, as do our data here, that circulating levels of *DHEAS* are much lower in chimpanzees than humans. Although they did not analyze changes across adulthood, their findings are generally concordant with those of our sample. Surprisingly they found marked differences between genus *Pan* and the other great apes. As ages at last birth and maximum lifespans are similar among the nonhuman great apes, we had assumed mechanisms of ovarian and somatic aging would be similar as well. But Bernstein and colleagues found otherwise. The level they calculated for gorillas (*Gorilla gorilla*)—again averaging both sexes—was only 34% that of *Pan*. Even more striking, orangutans (*Pongo abelii* and *P. pygmaeus* of both sexes) had average levels only 16% of *Pan*, the lowest average reported among catarrhines.

The differences in *DHEAS* levels across the nonhuman great apes suggest that androgens we have not investigated may be important in somatic maintenance. Lasley et al. (2012) further highlighted this possibility by suggesting the importance of another adrenal androgen, Androstenediol (Adiol), in perimenopausal women. They found (McConnell et al., 2012) that the transient increase in circulating *DHEAS* observed in perimenopausal women (Crawford et al., 2009) is accompanied by similar changes in the circulating levels of other adrenal androgens. Adiol is of particular interest because, in contrast to *DHEA/S*, it activates the estrogen receptor without intracrine conversion. Circulating at levels substantially higher than estrogen in postmenopausal women, Adiol may be vital to estrogenic bioactivity (Lasley et al., 2012).

Before concluding, we consider some limitations of our sample. Although often collapsed into age class averages, the individual variation in *DHEAS* levels in European, Australian, and American women is marked (see review in Enea et al., 2008). Yet Western women and captive chimpanzees do not represent the likely range of variation. For chimpanzees, captive conditions are known to affect ovarian hormone levels compared to those measured in the

wild (Emery and Whitten, 2003; Emery Thompson, 2005) and adrenal steroid levels may vary between captivity and the wild as well. In the same way, human variation may be even wider if non-Western subjects were included. Ovarian hormone levels are known to differ between industrial and traditional populations, with covariates including diet, work, and disease load (e.g., Ellison et al., 1993; Ellison, 1994; Jasienska and Jasienski, 2008; Vitzthum, 2008). Adrenal steroid levels may also differ.

If research into variation in male steroid levels is a guide to the magnitude of differences in women, differences in adrenal androgen levels may be smaller than differences in gonadal levels. Campbell et al. (2006, 2007) reported levels of both for Turkana men in nomadic and settled communities. Levels were significantly different for testosterone, but—except in the oldest subjects—*DHEAS* levels were not. On the other hand, Crawford et al. (2009) found dramatic differences in both *DHEAS* level and rate of change with age for American women of different ethnic groups between the ages of 42 and 52. Through those ages some of the women in their dataset had *DHEAS* levels that overlap our chimpanzee sample. However, little difference between African American and Caucasian women has been found in studies of *DHEAS* levels in younger adults (e.g., Kitabchi et al., 1999; An et al., 2001), and levels in these younger women are substantially higher than those of chimpanzees.

With those caveats we conclude that declines in circulating levels of *DHEAS* are not steeper in female chimpanzees than in women; but levels are substantially lower in chimpanzees; and the human difference from the other great apes is even larger than the difference from genus *Pan*. Contrasts among the other hominids raise additional questions, but also further distinguish the high *DHEAS* production in humans, a distinction consistent with the likelihood that this mechanism contributes to the extraordinary longevity of our own lineage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the keepers, veterinarians, and biological material procurement staff at Yerkes, the staff of the Biomarkers Core Lab, and CT Cloutier for bibliographic assistance.

Grant sponsor: NSF; Grant number: BCS—0717886; Grant sponsor: NIH; Grant numbers: P01AG026423 and P51RR000165.

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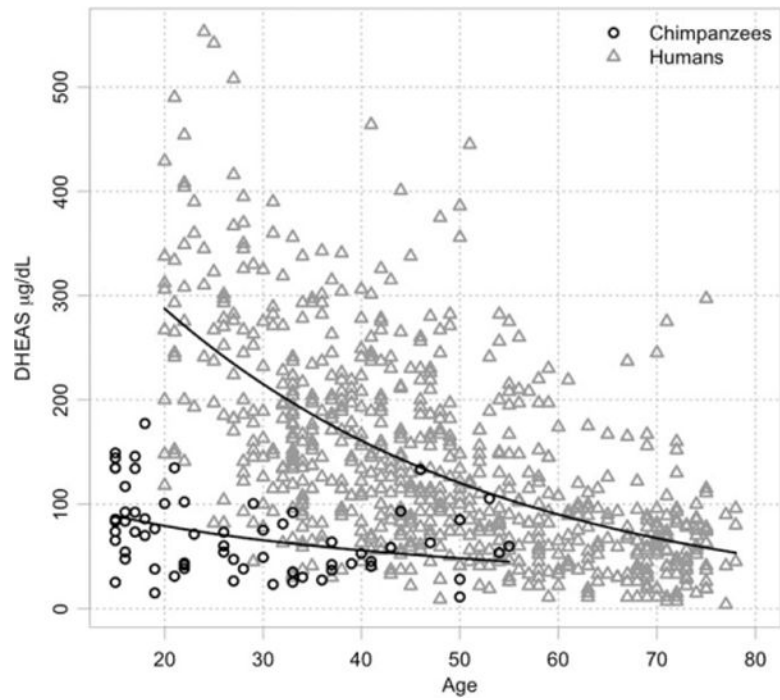


Fig. 1. Concentrations of DHEAS ($\mu\text{g/dL}$) as a function of age in both human ($n = 698$) and chimpanzee ($n = 65$) females. Lines represent best-fit models of DHEAS decline with age in humans and chimpanzees. See Table 1 for parameter estimates.

Parameter estimates, sample size, and estimated maximum DHEAS at the start of adulthood for models of DHEAS loss in human and chimpanzee females

TABLE 1

Sample	N	Functional form	A (95% CI)	B (95% CI)	Max. DHEAS (µg/dL)
Chimpanzee Table S1 (Supporting Information)	65	$y = A + B \cdot \ln(x)$	180.73 (114.71, 250.44)	-33.86 (-55.20, -13.64)	89.04
Human Table S2 (Supporting Information)	698	$y = e^{-(A + B \times x)}$	6.24 (6.10, 6.35)	-0.03 (-0.03, -0.03)	281.46
Human standard	11	$y = e^{-(A + B \times x)}$	6.14 (6.02, 6.25)	-0.03 (-0.04, -0.03)	254.68

In all three models, x corresponds to years of age. The second row is a model fitted to data from Ravaglia et al. (1996), Sulcova et al. (1997), and Davison et al. (2005) detailed in Table S2 (Supporting Information). The third row describes a model fitted to 11 age-class means reported by Orentreich and colleagues (1984), which serves as check on the generality of our individual-based human model. To estimate maximum DHEAS (i.e., expected DHEAS concentration at the start of adulthood) reported in the last column, we evaluated our chimpanzee model at 15 years and the human models at 20 years.

TABLE 2
Slope of declining human and chimpanzee *DHEAS* concentrations averaged over 5-year age intervals

Chimpanzees			Humans			Chimpanzee slope/human slope
Age range	N	Mean slope	Age range	N	Mean slope	
15-19	24	-1.60	20-24	31	-6.37	0.25
20-24	8	-1.23	25-29	48	-5.48	0.23
25-29	7	-1.01	30-34	75	-4.72	0.21
30-34	8	-0.85	35-39	73	-4.06	0.21
35-39	5	-0.73	40-44	92	-3.49	0.21
40-44	5	-0.65	45-49	85	-3.01	0.21
45-49	2	-0.58	50-54	62	-2.59	0.22
50-54	5	-0.52	55-59	60	-2.23	0.23
	-	-	60-64	44	-1.92	
	-	-	65-69	44	-1.65	
	-	-	70-74	64	-1.42	

To calculate an age interval's mean slope, we evaluated the relevant model (see Table 1 for parameter estimates) at the first and last years of the interval. We then subtracted the *DHEAS* estimate for the older age from that of the younger age and divided the resultant sum by five. The far right column shows the ratio of chimpanzee slope to human slope in each five-year interval following peak concentration.