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Senescent Decline in Serum Dehydroepiandrosterone Sulfate Concentrations in a Population of Wild Baboons

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The physiologic functions of dehydroepiandrosterone sulfate (DS), a precursor of androgens and estrogen and the most abundant steroid in the circulation, are unknown. Nevertheless, numerous studies have shown that low concentrations of DS are correlated with a variety of metabolic and cardiovascular diseases in human beings, and administration of DS to experimental animals is associated with protection from similar diseases. Thus, the marked decline in DS concentrations with age in human beings may be of considerable functional significance. However, because of the difficulties in studying any heterogeneous human population, it has been difficult to assess the extent to which the DS decline with age is confounded by any of a number of factors (e.g., smoking, level of activity, genetics, diet, medication and disease). We studied the effects of age on DS concentrations in a well-characterized population of wild yellow baboons living freely in a national park in East Africa. Study of these animals circumvents many of the confounds just noted. In examining animals ranging in age from juvenile status to old age, we observed a robust decline in DS concentrations with age. The magnitude of the decline is approximately equal in both sexes. In addition, the decline is similar in comparing two baboon groups which have fully natural diets with one group which forages heavily on garbage from people.

THE physiological function of dehydroepiandrosterone sulfate (DS), the weakly androgenic steroid secreted by the adrenal gland and the most abundant steroid in the circulation (Nestler et al., 1991), is unknown. Nevertheless, DS is of interest to gerontologists because of the decline in DS concentrations with age in human beings that constitutes the most dramatic and consistent of age-related change of any endocrine parameter (Yamaji and Ibayashi, 1969; Vermeulen, 1980; Zumoff et al., 1980; Orentreich et al., 1984; Barrett-Conner et al., 1986; Salvini et al., 1992).

This latter feature has been a particular stimulant for speculation by the above-cited authors about the role of DS, especially concerning its anti-aging potential. To test such ideas, it will be useful to, for example, examine whether DS profiles differ among aging people as a function of the severity of their various senescent impairments (i.e., the current emphasis by some gerontologists on comparing "successful" and "unsuccessful" agers [Rowe and Kahn, 1987]). Such comparisons are hampered by the considerable variability in human DS concentrations. Such heterogeneity can arise from numerous confounds, including level of activity (Diamond et al., 1989; Velardo et al., 1991), medication (Isojarvi, 1990; Isojarvi et al., 1990), diet (Bhathena et al., 1989), smoking (Barrett-Conner et al., 1986; Khaw et al., 1988; Salvini et al., 1992), alcoholism (Vlikorkala et al., 1988), disease confound (Lanzone et al., 1990; Villette et al., 1990; Becker et al., 1991), or genetics (Meikle et al., 1988).

The present report circumvents some of these confounds by examining the effects of aging upon DS profiles in a novel primate population, wild baboons living in a national park in East Africa. We observed a significant decline in basal DS concentrations with age.

METHODS

Life Histories and Social Organization

This research was conducted on yellow baboons, *Papio cynocephalus,* in Amboseli National Park of southern Kenya during 1989 and 1900. Baboons are among the largest, most sexually dimorphic, and most terrestrial of the monkeys. They live in semiclosed matrilocal social groups consisting of males and females of all ages. Baboons are omnivores that forage long distances daily in their savannah habitats.

Like most anthropoid primates, baboon females stay in their natal group throughout their lives, and from about 6 years of age until death they produce a single infant per gestation at 1–2 year intervals. After a subadult period from 6–8 years of age, most males leave their natal group and, if successful, reproduce in one or a succession of other groups; emigration is most commonly into nearby groups (Samuels and Altmann, 1991). Under stable demographic conditions, animals over 6 years old usually constitute half of the 60 or so animals in a group, and a few of each sex are usually over 16 years old (Altmann and Altmann, 1979; Strum and Western, 1982; Altmann et al., 1985).

Subjects and Observational Methods

The subjects were the members of three baboon groups whose adjacent home ranges include Amboseli National Park and who are a subset of the larger Amboseli basin baboon population. All members of the three groups are identified by

distinctive physical characteristics and have been part of longitudinal research projects. The histories of almost all females and of those males that were born into one of these study groups have been known since birth (see, e.g., Altmann et al., 1988; Altmann and Muruthi, 1988). For animals born into the study groups, birth dates are known within a few days, and usually to the day, based on an almost-daily census and neonatal assessment records (Altmann, 1980). Ages of immigrant males in each group are usually known, at least to within the year, either because they were born into one of the other study groups or because they had been individually identified in their previous group during periodic censuses of the groups adjacent to the study groups. In some cases, males are first identified when they immigrate into a study group and age is estimated based on extensive information from visual morphological assessments during maturation and aging of known-age animals in study groups.

Dietary Differences Among Groups

Although the three groups occupy overlapping ranges and are part of a single dispersal pool for the males, the groups have different food resources available. Whereas two groups are wild-foraging, the range of the third group includes the garbage dump of a tourist lodge, providing an abundant and readily accessible food supply. While adult females of the three groups have similar average daily caloric intakes (Muruthi, 1989), they differ considerably in activity levels. Females of the partially garbage-feeding group spend more time resting and socializing, less than half as much time feeding or traveling, and expend approximately 16% less energy than do those of the wild-foraging groups (Altmann and Muruthi, 1988; Muruthi et al., 1991). Comparable data are not yet available for other age-sex classes.

Acquisition of Blood Samples

Plasma was obtained by anesthetizing subjects with Telazol (tiletamine hydrochloride and zolazepam) (250 mg for older juveniles and adults [male weight range: 16–38 kg; female weight range: 10–24 kg] and one fourth to one half that for smaller animals); it was injected from a propelled syringe fired from a blowgun at 10m. No pregnant females were darted except a few in the first trimester. Animals were darted only when their backs were turned, to preclude anticipatory stress. All subjects were darted between 0730 and 1030 h during July–October, 1989 and 1990, to control for seasonal and circadian hormone fluctuations. A blood sample was obtained as rapidly as possible; in all cases, this was within 15 minutes of darting. Darting itself is not sufficiently stressful to increase cortisol secretion in baboons; rather, it is the disorientation just before anesthetization that is stressful (Sapolsky, 1982). Thus, the sample taken probably reflects basal concentrations of various steroid hormones.

Animals recovered in a cage near their group and were released the following morning when fully conscious. No loss of habituation to observers or difficulty in rejoining troops was observed. A total of 62 males and 46 females were anesthetized and sampled in this manner.

Determination of DS Concentrations

DS concentrations were determined by radioimmunoassay according to a modification (Orentreich et al., 1984) of the method of Buster and Abraham (1972). Samples were measured in a single assay with a coefficient of variation of <4%. In this report, both DS and dehydroepiandrosterone (D) are measured as total "DS," since the measurement of D separately would yield little biological information. This is because D secretion is episodic, D is rapidly converted to DS, and the level of DS is more than 100 times larger than D, collectively. The body normally converts D to DS or DS to D to maintain its own equilibrium.

Data Analysis

We used the general linear models procedures (GLM) in SAS (SAS Institute, 1988) to examine the extent to which sex, feeding condition, age, and interactions among these accounted for variability in DS values. Heterogeneity of variance was reduced, though not eliminated, with transformation of the data, and use of single values per individual in a natural population necessitates compromise to an ideal of a statistically balanced or, preferably, longitudinal design.

RESULTS

Figure 1 presents DS concentrations in (top) female and (bottom) male baboons. Values were within the range previ-

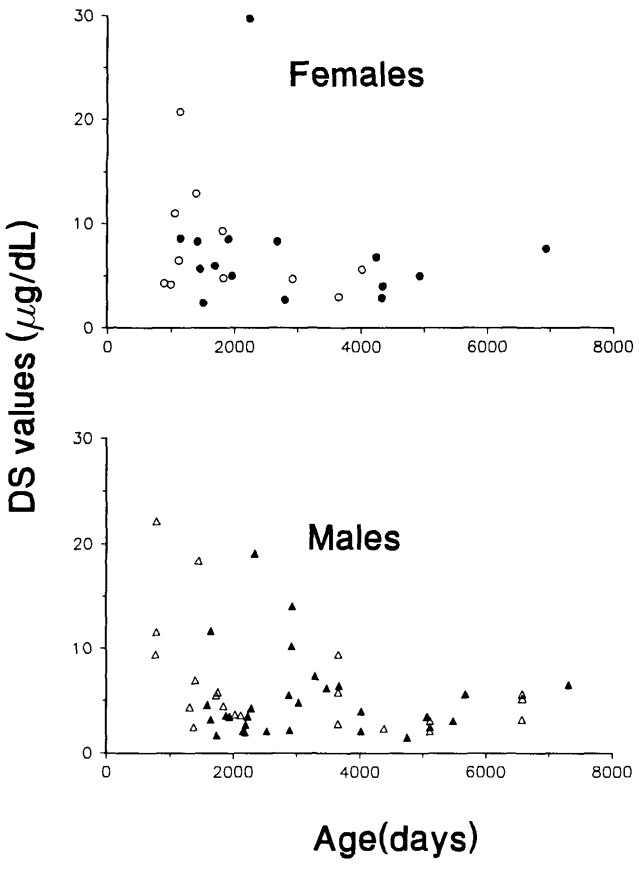

Figure 1. DS concentrations (in μg/dl) as a function of age among the female baboons (top) and male baboons (bottom) of the three groups studied. Closed circles and triangles are data from wild-foraging animals; open circles and triangles are data from garbage-foraging animals. Age distributions did not differ as a function of diet.

ously reported by Cutler (1978), approximately an order of magnitude lower than seen in humans (cf. Orentreich et al., 1984; Barrett-Conner et al., 1986), and about a fourth of those seen in captive, singly housed rhesus monkeys (based on comparison of the adults in this population with the adult rhesus monkeys studied by Kemnitz et al., 1989). Females tended to have slightly higher concentrations than males in each feeding condition, and wild-feeding animals of each sex tended to have slightly higher values than partially garbage-feeding ones. Nonetheless, neither feeding condition nor sex (nor interactions) was significant when added to the model. Only feeding condition approached significance ($.05 < p < .10$).

Although DS levels were highly variable at all ages, DS concentrations declined significantly in both sexes with age (adj. $r^2 = .08$; $p < .008$; logDS = 2.02–0.045 y, where y is age in years). In males, concentrations declined an average of 8% per year (calculations based on curve fitting the mean of the log of the data as shown in Table 1 [Orentreich et al., 1984]), and values in the most aged animals were approximately a fifth of those of the juveniles that made up the youngest group. For the females, concentrations declined 7% per year and values of the aged animals were about one half those of the young animals.

DISCUSSION

The function of DS is unclear; nevertheless, the weakly androgenic steroid has striking effects on a broad array of disease processes and longevity. Administration of DS to experimental mice prevents obesity (Yen et al., 1977), lowers cholesterol concentrations (Ben-David et al., 1967), decreases mortality due to autoimmune disorders (Matsunaga et al., 1989), and increases resistance to cancer (Schwartz et al., 1986). The potential physiologic relevance of these laboratory observations is strengthened by reports that in people, low concentrations of DS are associated with hypercholesterolemia (Sonka et al., 1968; Lopez-S et al., 1976), hypertension (Nowaczynski et al., 1968), Alzheimer's disease (Sunderland et al., 1989), more severe incidences of HIV infection (Jacobson et al., 1991), cardiovascular disease (Marmorston et al., 1957; Rao, 1970; Herrington et al., 1990), and greater mortality due to cardiac disease (Zumoff et al., 1982; Barrett-Conner et al., 1986). When these findings are combined with the marked decline in DS with age in human beings cited earlier, DS concentrations are speculated to be discriminators of life expectancy and of successful aging (Lopez-S, 1984; Barrett-Conner et al., 1986).

However, efforts to study the interactions of aging and effects of DS are confounded in human studies in a number of ways. Our study of a wild population of nonhuman primates circumvents some of these problems. Within the troops subsisting on natural diet, diet and level of activity are more homogeneous than in a similar-sized population of Westernized humans. Obviously, baboons do not have the confounds of medication, smoking, or alcohol consumption common to many people. Finally, the aged baboons were probably in relatively better health than aged Westernized humans, making it less likely that the decline in DS concentrations was an artifact of coincident disease. This is because aged wild baboons in less than robust health will not survive the exigencies of predators and the physical demands of foraging (i.e., the survivorship curve among wild baboons is less rectangular than in Western societies).

Among these baboons, we observe an age-related decline in DS concentrations in both sexes and in animals having both a natural and semi-natural diet. Although concentrations were far lower than in human beings (cf. Orentreich et al., 1984; Barrett-Conner et al., 1986), the slope of the decline was roughly equivalent to what we have observed previously in human levels from ages 15 to 70 (Orentreich et al., 1984). The highest DS concentrations occurred in the youngest baboons studied; animals of this age (approximately 3 years) are typically classified as juveniles. By adolescence (approximately 4.5–7.5 years, or 1600–2700 days), DS concentrations had declined approximately 25%. By old age (approximately 15 years or older [>5500 days]), levels in the few surviving males were approximately 75% lower than those of the younger animals. In human populations, DS concentrations decline postnatally and rise from approximately 7 years of age until late adolescence/early adulthood (DePeretti and Forest, 1978) before starting to decline throughout the rest of the life span; because of issues of safety to these animals, we did not anesthetize animals young enough to have determined whether a similar maturational trend occurs in the prejuvenile baboons.

We noted only a weak trend toward higher DS concentrations among females, similar to a trend reported in nonobese captive rhesus monkeys (Kemnitz et al., 1989). We also noted only a trend toward lower DS concentrations in the

Table 1. Dehydroepiandrosterone Sulfate (DS) in Baboons, Measured in μg/dl

Age Range (Days)	Average Age (Days)	Males		Females	
		Mean DS	Geometric Mean DS[a]	Mean DS	Geometric Mean DS[a]
501–1500	1000	10.70	8.59	9.13	8.03
1501–2500	2000	4.99	4.06	6.00	5.49
2501–3500	3000	6.56	5.49	5.23	4.71
3501–4500	4000	4.70	4.11	4.45	4.20
4501–5500	5000	2.61	2.52	NA[b]	NA

[a]See Orentreich et al., 1984.

[b]NA = not available, because of insufficient numbers of animals in that age group.

garbage-feeding monkeys, despite their considerable increase in body fat (Altmann et al., 1993). This seemingly contrasts with studies of captive female rhesus monkeys, among whom obesity was associated with a significant decrease in DS concentrations (Kemnitz et al., 1989). However, the obese monkeys in that study were older than nonobese animals. In addition, despite considerably greater body size and fatness among the garbage-feeding baboons when compared to the wild-feeding ones, fatness levels are still low compared to either human beings or singly-housed rhesus; morphometric and physiologic measures indicate that the garbage-feeders more closely resemble the "nonobese" animals in the captive studies (Kemnitz et al., 1989; Altmann et al., 1993).

The decline in human DS concentrations with age represents decreased DS production rather than impaired clearance (Vermeulen, 1980); however, this does not reflect a general decline in adrenocortical steroidogenesis. For example, there is a trend toward enhanced glucocorticoid secretion in aged human beings (cf. Sapolsky, 1990), as well as among the aged baboons of this wild population (Sapolsky and Altmann, 1991).

In conclusion, we have observed a robust decline in circulating DS concentrations with age in a population of wild baboons among whom many of the confounds found in human aging studies are eliminated. This decline is striking, given the exigencies of selection against long life among these wild animals; i.e., the rare aged baboons in this population are atypical animals, perhaps good candidates for the label of "successful agers."

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