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Review

Dehydroepiandrosterone sulfate (DHEAS) as an endocrine marker of aging in calorie restriction studies

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ABSTRACT

The adrenal steroid, dehydroepiandrosterone sulfate (DHEAS), is generally regarded as being a reliable endocrine marker of aging, because in humans and nonhuman primates its circulating concentrations are very high during young adulthood, and the concentrations then decline markedly during aging. Despite promising results from early studies, we were recently surprised to find that caloric restriction (CR) did little to prevent or delay the decline of DHEAS concentrations in old rhesus macaques. Here we summarize the use of circulating DHEAS concentrations as a biomarker of aging in CR studies and suggest reasons for its limited value. Although DHEAS can reliably predict aging in animals maintained on a standard diet, dietary manipulations may affect liver enzymes involved in the metabolism of steroid hormones. Consequently, in CR studies the reliability of using DHEAS as a biomarker of aging may be compromised.

1. Introduction

According to the US Census Bureau, almost 20% of the US population is expected to be 65 years of age and older by 2030. Clearly, this demographic change will have a major impact on society's future health care needs and on the economy of the country. Consequently, there is an immediate need for a better understanding of mechanisms that underlie normal and pathological human aging, and for the development of safe and effective therapies. To date, however, dietary caloric restriction (CR) remains the only reproducible, non-genetic intervention that has been shown to limit or delay deleterious aging processes in mammals. A moderate (30–50%) reduction in caloric intake, without malnutrition, has been shown to extend average and maximal lifespans, to reduce the incidence of age-related diseases, and to maintain healthy physiological function later into life in short-lived species (Weindruch and Sohal, 1997; Weindruch and Walford, 1988).

The first report of the lifespan extending effects of CR appeared over 75 years ago (McCay et al., 1935). Since then, numerous studies have advanced CR research, and have generated progress toward elucidating possible mechanisms underlying the anti-aging benefits of CR (Bartke et al., 2001; Gredilla and Barja, 2005; Heilbronn and Ravussin, 2003). Despite the large body of evidence describing the benefits of CR in short-lived species, including yeast, nematode worms, flies, fish, dogs, and rodents (Barrows and Kokkonen, 1982; Weindruch and Walford, 1988), it remains to be determined whether CR is relevant to human or non-human primate aging (Colman et al., 2009; Lane, 2000; Lane et al., 1997b, 2001; Masoro, 2000; Mattison et al., 2003; Mattison et al., 2005, 2012; Ramsey et al., 2000; Roth et al., 2001; Roth et al., 2004; Weindruch and Sohal, 1997).

2. The rhesus macaque as a translational animal model for biogerontological studies

Like humans, rhesus macaque monkeys (*Macaca mulatta*) are long-lived primates, and they show many similarities in their anatomy, physiology behavior, and genetics (Gibbs et al., 2007; Messaoudi et al., 2011). Consequently, rhesus monkeys are regarded as pragmatic animal models for studying mechanisms that underlie normal and pathological human development and aging. Their use as translational animal models

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has many advantages. For example, rhesus monkeys can be maintained under carefully controlled environmental conditions (e.g., photoperiod, temperature, diet, and medication). In addition, animals of a specific age, size, sex, and genetic characteristic can be selected, thereby eliminating extraneous variables and self-selection bias that are typically associated with human clinical trials. Moreover, because the timing of necropsies can be carefully controlled in rhesus macaques, high quality postmortem RNA samples can be collected for gene expression profiling.

Cross-sectional and longitudinal studies of the effects of CR on longevity and aging in the rhesus monkey began in 1987 (Ingram et al., 1990). However, with a maximum lifespan of ~40 years (Bliwise, 2000; Bodkin et al., 2003; Roth et al., 2004), several more years of study will be necessary before a consensus is reached on possible CR effects on rhesus lifespan. On the one hand, ongoing studies at the Wisconsin National Primate Research Center (WNPRC) and at the National Institute on Aging (NIA) have both demonstrated health benefits associated with CR in adult rhesus monkeys (Colman et al., 2009; Mattison et al., 2012). On the one hand, some discrepancies exist between the findings of these two studies; improved survival was reported for the CR monkeys in the WNPRC study (Colman et al., 2009) but not in the NIA study (Mattison et al., 2012), suggesting that there may be separation between health benefits, morbidity, and mortality. Consequently, the availability of relevant biomarkers of aging are critical to furthering the understanding of the effects of CR on the aging process, especially to assess effects in long-lived species like primates (Ingram et al., 2001; Nakamura et al., 1994, Nakamura et al., 1998).

3. Adrenal steroids as biomarkers of aging

The adrenal steroids – cortisol, dehydropiandrosterone (DHEA) and DHEA sulfate (DHEAS) – play an important role in regulating responses to stress. Elevated cortisol suppresses the immune system, breaks down tissues and has a general catabolic effect; whereas, DHEA and DHEAS counter-balance the effects of cortisol by activating the immune system and building up tissues. Importantly, cortisol and DHEAS are two of the most abundant steroids in the circulation of adult humans and rhesus monkeys. Furthermore, DHEAS shows a profound age-related decrease, while cortisol levels remain constant or increase (Downs et al., 2008; Labrie et al., 1997; Lane et al., 1997a; Orentreich et al., 1992; Roth et al., 2004; Sorwell and Urbanski, 2010; Urbanski and Sorwell, 2012; Urbanski et al., 2004). Based on longitudinal DHEAS measurements across the life span of adult Japanese macaques, this age-related decline appears to be gradual rather than occurring precipitously during old age (Sorwell et al., 2012); consequently, it is difficult to link it causally to a specific age-associated physiological event. Nevertheless, there is evidence that DHEA and DHEAS play an important role in attenuating some of the deleterious effects of elevated cortisol levels that are associated with chronic stress. For example, in aged animals, the DHEA:cortisol ratio shows a marked age-associated decline, and it has been suggested that the unopposed high cortisol levels play a key role in age-associated cognitive decline, impaired attention span, and loss of long-term memory (Karishma and Herbert, 2002; van Niekerk et al., 2001). In contrast, in young adults the highly elevated DHEA and DHEAS levels help to moderate these negative effects of cortisol.

Because of the profound age-related decline in circulating DHEAS levels, in both humans and rhesus monkeys, there has been interest in using DHEAS as a potential biomarker of aging progression in calorie-restriction studies (Heilbronn et al., 2006). Early efforts were extremely promising. A major study, initiated by the National Institute on Aging (NIA, Baltimore, USA), found that over a 3-year period circulating DHEAS levels declined by over 30% in control rhesus monkeys but by only 5% in age-matched CR animals (Lane et al., 1997a, 1999, 2001). Although the animals were only young adults at the time of the report, there was great optimism that prolonged CR would significantly block or delay the marked age-related attenuation of DHEAS levels that is characteristic of old age in humans and rhesus monkeys. Unfortunately, these studies were conducted before it was well established that circulating DHEAS levels in rhesus monkeys have a well-defined 24-hour pattern, with a peak early in the morning and a nadir in the late evening. Consequently, there was concern that blood samples collected at a single time-point during the day from anesthetized monkeys might not adequately control for the diurnal variation in release of DHEA and DHEAS from the adrenal glands. Furthermore, it remained to be determined if long-term CR resulted in sustained elevation of circulating DHEAS levels.

4. Recent updates on DHEAS as a biomarker of aging in calorie restriction studies

Two important studies were performed recently to test the hypothesis that circulating DHEAS levels reliably reflect the degree of aging in CR studies. In the first study, young (~11 years old) and old (~27 years old) male rhesus monkeys were either subjected to 30% calorie restriction for 4–5 years or were maintained on a standard diet (Downs et al., 2008; Urbanski et al., 2004). Importantly, each animal was fitted with a subclavian vein catheter, which enabled remote serial collection of blood without disturbing the animals (Urbanski, 2011). Measurement of DHEAS in plasma samples, collected hourly across the day and night, showed a clear-cut 24-hour rhythm. Peak levels were detected in the morning soon after the animals woke up and nadir levels occurred in the evening a few hours into the dark (Fig. 1). As expected, overall mean DHEAS levels were markedly lower in the old animals. Importantly, however, there was no significant difference between the CR and the age-matched control animals. Moreover, contrary to expectations, short-term CR did not cause an elevation of plasma DHEAS levels in the old CR. Overall, these results are consistent with the findings from a recent human study in which 6 months of CR had no obvious effect on circulating DHEAS levels (Heilbronn et al., 2006). It should be noted, however, that the CR paradigm in our monkey study was initiated when the animals were already old (i.e., approximately 22 years old) and was carried out for only 4–5 years. Therefore, the results of this experiment,

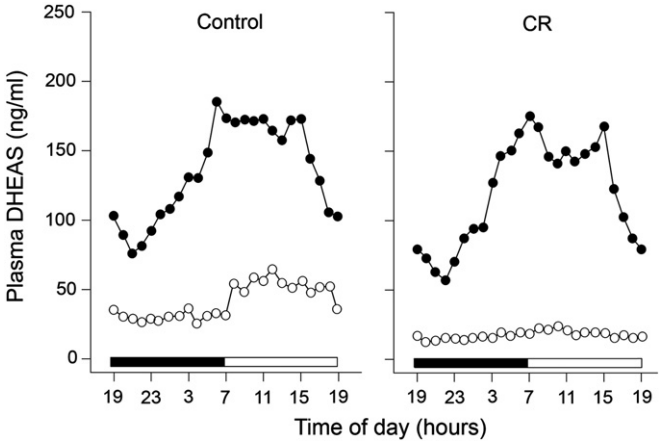

Fig. 1. Effect of age and dietary manipulation on the circulating 24-h patterns of DHEAS in male rhesus macaques maintained at the ONPRC. Left panel: mean plasma DHEAS profiles from young (~11 years old, n=5) and old (~27 years old, n=6) controls are represented by black and white symbols, respectively. Right panel: mean plasma DHEAS profiles from age-matched young (n=5) and old (n=4) monkeys subjected to short-term calorie-restriction (4–5 years; CR) represented by black and white symbols, respectively. The serial blood samples (1 ml) were collected remotely each hour via a subclavian vein catheter, as described (Urbanski, 2011). The *horizontal black and white bars* on the abscissas correspond to the 12L:12D lighting schedule. Two-way analysis of variance (ANOVA) followed by the Newman–Keuls test was used to evaluate group differences (using age and diet as variables). In both the controls and CR monkeys there is a significant ($P<0.01$) age-related decrease in overall mean DHEAS levels. Importantly, DHEAS levels in the old CR monkeys were not higher than in the age-matched controls.
Data adapted from Downs et al. (2008).

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