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Age- and gender-associated changes in the concentrations of serum TGF-1β, DHEA-S and IGF-1 in healthy captive baboons (*Papio hamadryas anubis*)

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ABSTRACT

Age-related changes in the concentration of factors like TGF-1β, DHEA-S and IGF-1 may increase the risk of disease and illnesses in advanced life. A better understanding of these changes would aid in the development of more appropriate treatments and/or preventative care for many conditions associated with age. Due to their similar immune system and vulnerability to pathogens, baboons are an ideal model for humans. However, little research has been done examining the general effects of age in baboons. Therefore, we wanted to further examine the effects of aging in baboons by determining the age-dependent changes in serum TGF-1β, DHEA-S and IGF-1 concentrations. Blood samples were collected during routine health checks in 113–118 captive baboons. In addition, longitudinal samples from 23 to 27 adult individuals were collected an average of 10.7 years apart. Both age and gender influenced the concentrations of serum TGF-1β and IGF-1. When both genders were analyzed together, TGF-1β increased 16.1% as adults, compared to younger and older animals, but male and female baboons showed a slightly different temporal pattern of change. IGF-1 decreased with increasing age and males had a 30% greater concentration of IGF-1 than did females. While there was no effect of gender among our population, serum DHEA-S was negatively correlated with age, decreasing by 51.6% in the oldest animals. There were no effects of age or gender on serum IGFBP-3. In longitudinal samples collected from the same individuals, the concentrations of TGF-1β, DHEA-S and IGF-1 were reduced with age. The results presented herein provide additional knowledge of the aging process in baboons and further validate the use of this species as an appropriate model for aging in humans.

1. Introduction

Transforming growth factor-1β (TGF-1β), insulin like growth factor-1 (IGF-1), and the adrenal steroid hormone, dehydroepiandrosterone-sulfate (DHEA-S) are important factors that are essential for normal physiological processes. In the aging human, there is evidence that changes in the concentration of factors like TGF-1β, DHEA-S and IGF-1 may increase the risk of disease and pathological conditions seen among the elderly. In order to develop treatments and preventatives for chronic conditions that occur in aged individuals, a better understanding of changes that occur during the aging process and its impact on biological systems is required.

Transforming growth factor-1β is an anti-inflammatory cytokine member of the prototypic TGF-β superfamily. Although originally found to induce anchorage-independent growth in fibroblasts (Roberts et al., 1981), it is now known to be a multifunctional protein that plays an important role in many physiological systems (Letterio and Roberts, 1998). Mice null for TGF-1β show impairment in the development and regulation of the immune system as well as in the maintenance of immunological homeostasis. Furthermore, specific endocrine, paracrine and autocrine actions were discovered for TGF-1β (Letterio and Roberts, 1996). Circulating concentrations of TGF-1β have been found to both decrease and increase with age in humans. Okamoto et al., found that serum concentration TGF-1β were decreased in adults 21–67 years of age compared to children 1–14 years of age (Okamoto et al.,

Abbreviations: TGF-1β, transforming growth factor-1β; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; IGF-1, insulin like growth factor-1; IGFBP-3, insulin like growth factor binding protein-3; IL, interleukin; Ig, immunoglobulin.

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2005). Similarly, in adults 40–79 years of age, serum concentrations declined in an age-dependent manner (Lin et al., 2009b). However, in centenarians, serum TGF-1β concentration was increased when compared to younger adults (Carrieri et al., 2004), perhaps suggesting that high concentrations of TGF-1β are beneficial during extreme old age. Research with human diseases has shown that a greater concentration of TGF-1β is associated with a higher risk of diseases such as heart failure, lung cancer and metastatic prostate cancer in adults (Glazer et al., 2012; Hou et al., 2013; Shariat et al., 2001). It can also exhibit differing roles in normal compared to diseased tissues. In normal breast tissue it is a potent inhibitor of proliferation, but TGF-1β appears to promote proliferation during the development of breast cancer (Moses and Barcellos-Hoff, 2011).

Dehydroepiandrosterone and its more stable sulfate ester, DHEA-S, are mainly produced by the zona reticularis in the adrenal cortex. They are an important precursor of sex steroids, and consequently, adrenal production increases during adrenarche (Hazeldine et al., 2010; Labrie, 2010; Maninger et al., 2009; Savineau et al., 2013). In people, maximal serum DHEA-S concentrations are reached in the thirties then begin to decline considerably, such that by 70 years of age, DHEA-S concentrations are only approximately 20% of their peak values (Hazeldine et al., 2010; Labrie, 2010; Maninger et al., 2009; Savineau et al., 2013). In addition to its role as a sex steroid precursor, DHEA-S also functions as an important regulator of the immune system. For example, studies *in vitro* and *in vivo* found that treatment with DHEA-S increased mitogenic responses by T and B lymphocytes and cytotoxicity of natural killer cells (Khorram et al., 1997; Solerte et al., 1999). High doses of DHEA can have both immune stimulatory and anti-glucocorticoid effects *in vitro* and *in vivo* (Buford and Willoughby, 2008; Hazeldine et al., 2010). Exogenous DHEA-S can also exhibit either anti- or pro-oxidant effects, depending on the dose and on tissue specificity. In the cardiovascular system, for instance, its main effects appear to be anti-oxidant (Savineau et al., 2013).

The growth hormone–IGF-1 axis has been known to be essential for body growth and maintenance for decades. It is necessary for both the transition of fetus to neonate and for continued normal development after birth. Insulin-like growth factor-1 knockout mice are infertile and have considerably impaired growth (Oberbauer, 2013; Puche and Castilla-Cortazar, 2012). In people, the concentration of serum IGF-1 peaks around the peri-pubertal period and then begins to continuously decline after adulthood (Bartke, 2008; Deak and Sonntag, 2012; Sonntag et al., 2005). Like TGF-1β and DHEA-S, IGF-1 also affects immune function and the aging process. *In vitro*, treatment with IGF-1 increased the production of immunoglobulin-E (Ig) and IgG4, and enhanced expression of type II IgE receptors on human B cells (Kim et al., 2003; Kimata and Fujimoto, 1994). Its major binding protein in blood, IGFBP-3, aids in the transport and modulation of circulating IGFs and is itself a negative acute phase protein. In rodents, the administration of lipopolysaccharide endotoxin decreases both IGFBP-3 in serum and its synthesis in the liver (Priego et al., 2003). There is also evidence that IGFBP-3 has potent anti-proliferative and pro-apoptotic effects independent of IGFs. These effects may be important in tumor development and progression (Baxter et al., 2000; Butt and Williams, 2001).

Although aging may be studied in humans using clinical subjects, animal models for humans are highly beneficial by providing a greater supply of subjects and ease of manipulation. To date, the majority of general aging studies using animal models have been done in invertebrates and rodent species. However, large animal models offer distinct advantages over rodents and invertebrates due to a closer similarity in genetics and physiology to more complex mammals. Captive non-human primates (NHP) provide an excellent model for humans. In particular, baboons are an ideal model, as they share greater similarity in immune system than other old world monkeys, with four IgG antibody subclasses and they demonstrate similar vulnerability to pathogens as people (Attanasio et al., 2002; Kennedy et al., 1997; Murthy et al., 2006; Shearer et al., 1999; Wolf et al., 2006). However, beyond their use for specific disease models, little research has been done examining the general effects of age using the baboon model.

A previous study by our laboratory found that aged baboons showed age-associated inflammatory changes similar to what had been found in people and rodents (McFarlane et al., 2011). In that study, we found that the serum aging biomarkers, C-reactive protein, IL-6, and IL-6:IL-10 ratio increased with age in captive baboons. Furthermore, cytokine response of peripheral blood mononuclear cells and in whole blood increased in an age-dependent manner in baboons (McFarlane et al., 2011). Therefore in the present study, we wanted to further examine the effects of aging in baboons by determining the age dependent changes in serum concentration of the aging biomarkers TGF-1β, DHEA-S and IGF-1.

2. Materials and methods

2.1. Animals for population study and sample collection

All captive baboons were held at the Baboon Research Resources, Department of Comparative Medicine, University of Oklahoma Health Sciences Center (BRR-OUHSC). Animals were housed outdoors in hierarchical troops of approximately 60–80 animals per troop and were fed a commercial diet of monkey chow and fresh fruits and vegetables. Water was provided ad libitum. Saphenous venous blood was collected during routine annual health checks from 113 to 118 captive baboons. Coagulated blood was centrifuged at 500*g* for 15 min and serum was collected and stored on ice until transported to the laboratory. Samples were then frozen at −80 °C until analysis. 93–96 Females and 20–22 males ranging in age from 2 to 26.7 years old were included in the study. The mean age of the study groups was 12 years. Table 1A provides a summary of the demographic information for the animals included in the population study. All procedures with animals were approved by the University of Oklahoma's Animal Care and Use Committee.

2.2. Longitudinal study in adult baboons

To determine the effects of age on TGF-1β, DHEA-S and IGF-1 within the same animal, multiple samples were collected overtime from the same individuals. Samples were collected at two different ages in 23–27 animals. All animal were considered adults and ranged in age from 4.6 to 26.7 years old when samples were collected. Baboons averaged 9.3 ± 2.9 years of age at first sample collection and 20.3 ± 3.5 years old at second sample collection, with a mean difference of 10.71 ± 2.9 years between collections. Archived and fresh samples were frozen and held at −80 °C until analysis. A summary of the demographic information for the longitudinal study animals is included in Table 1B.

2.3. Radioimmunoassays and enzyme-immunoassays

DHEA-S was measured in serum using a commercial single-antibody radioimmunoassay (RIA) for human DHEA-S (Siemen's Coat-a-Count DHEA-Sulphate RIA kit, Siemens Medical Solutions USA, Inc., Los Angeles, CA). Assay sensitivity is 9 ng/ml and cross-reactivity of the antibody with DHEA, androsterone, androstenedione, estrone, progesterone, testosterone and 17β-estradiol is 100% 20%, 6%, 0.4%, 0.2%, <0.1% and < 0.1%, respectively. TGF-1β was measured by a commercially available double-antibody sandwich enzyme-immunoassay (EIA) for human TGF-1β (R&D Systems,