Psychoneuroendocrinology (2011) 36, 1441—1452

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Genetic and environmental effects on diurnal dehydroepiandrosterone sulfate concentrations in middle-aged men

Elizabeth C. Prom-Wormley [a,*], Timothy P. York [a], Kristen C. Jacobson [b], Lindon J. Eaves [a], Sally P. Mendoza [c], Dirk Hellhammer [d], Nicole Maninger [c], Seymour Levine [g], Sonia Lupien [h], Michael J. Lyons [i], Richard Hauger [e,f], Hong Xian [j], Carol E. Franz [e], William S. Kremen [e,f]

[a] *Virginia Institute for Behavioral and Psychiatric Genetics, Virginia Commonwealth University, United States*
[b] *Department of Psychiatry, University of Chicago, United States*
[c] *California National Primate Research Center, University of California Davis, United States*
[d] *Department of Psychobiology, University of Trier, Germany*
[e] *Department of Psychiatry, University of California San Diego, United States*
[f] *VA San Diego Healthcare System, United States*
[g] *Department of Psychiatry, University of California Davis, United States*
[h] *Mental Health Research Centre Fernand Seguin, Hôpital Louis-H Lafontaine, Université de Montréal, Canada*
[i] *Department of Psychology, Boston University, United States*
[j] *Department of Internal Medicine, Washington University, United States*

Received 12 August 2010; received in revised form 27 January 2011; accepted 29 March 2011

KEYWORDS
DHEAS;
Diurnal concentrations;
Genetics;
Twin study;
Aging;
Men

Summary
Background: Dehydroepiandrosterone sulfate (DHEAS) is important for its association with immune system function and health outcomes. The characterization of the genetic and environmental contributions to daily DHEAS concentrations is thus important for understanding the genetics of health and aging.
Methods: Saliva was collected from 783 middle-aged men (389 complete pairs and 5 unpaired twins) as part of the Vietnam Era Twin Study of Aging. Samples were taken at multiple specified time points across two non-consecutive days in the home and one day at the study sites. A twin modeling approach was used to estimate genetic and environmental contributions for time-specific and average DHEAS concentrations.
Results: There was a consistent diurnal pattern for DHEAS concentrations in both at-home and day-of-testing (DOT) measures, which was the highest at awakening and decreased slightly

* Corresponding author at: Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, PO Box 980126, Richmond, VA 23298-0126, United States. Tel.: +1 804 828 8154; fax: +1 804 827 0018.
E-mail addresses: ecpromwormle@vcu.edu, ecprom@vcu.edu (E.C. Prom-Wormley).

0306-4530/$ — see front matter. Published by Elsevier Ltd.
doi:10.1016/j.psyneuen.2011.03.018

throughout the day. Heritability estimates were significant for measures at 10 am, 3 pm and bedtime for the in-home days and at 10 am and 3 pm on the DOT, ranging between 0.37 and 0.46. *Conclusions:* The significant heritability estimates later in the day reflect time-specific genetic effects for DHEAS, compared with prior twin and family designs studies which frequently used averaged morning-only measures. Additive genetic influences on DHEAS concentrations were consistent between at-home and DOT measures.
Published by Elsevier Ltd.

Introduction

Dehydroepiandrosterone (DHEA) and its sulfated metabolite (DHEAS) are the most abundant products secreted by the zona reticularis of the adrenal cortex (Orentreich et al., 1984). Like cortisol, DHEA and DHEAS are secreted from the adrenal cortex in response to adrenocorticotrophin (ACTH) stimulation (Pavlov et al., 1986; Parker et al., 1996). DHEA is the precursor for approximately 50% of the androgens produced in adult men (Brown et al., 2002), underscoring the importance of this hormone in the production of sex steroids. DHEA is converted to the more stable DHEAS by DHEA sulfotransferase (HST, SULT2A1) and DHEAS easily becomes DHEA via steroid sulfatase (STS) (Kroboth et al., 1999). DHEA is considered to be a biologically active hormone, and many studies focus on the association between DHEA and health-related outcomes. However, DHEAS may have a distinct role from DHEA in the etiology of disease, particularly in the regulation of the immune system (Radford et al., 2010) and in neuroprotection (Maninger et al., 2009). Further, DHEAS is thought to be the circulating storage pool for DHEA because DHEAS has a half-life of 10—20 h, while the half-life of DHEA is 1—3 h (Rosenfeld et al., 1975). Similarly, the clearance rate of DHEAS is much slower than that of DHEA (Longcope, 1996). There is a need to study the causes of the individual variation of diurnal DHEAS production, which is anticipated to be caused by genetic and environmental influences because it is the most abundant steroid hormone in the body, it is necessary for sex hormone synthesis, and is associated with diseases related to aging.

The roles between DHEAS in the etiology of chronic disorders related to aging

Low DHEAS concentrations have been associated with coronary artery disease, cardiovascular disease, non-insulin dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosis, pemiphigoid/pemphigus, and HIV/AIDS, indicating the relationship between DHEAS concentrations and the immune system (Chen and Parker, 2004). Both DHEAS and cortisol modulate the immune system, although DHEAS generally acts to enhance while glucocorticoids suppress immune function (Butcher et al., 2005; Chen and Parker, 2004). DHEAS has recently been reported to have immunostimulatory effects, increasing superoxide generation in primed human neutrophils in response to pathogens (Radford et al., 2010). Additionally, DHEAS has anti-inflammatory effects through the inhibition of NF-κB activation (Iwasaki et al., 2004).

Lower concentrations of salivary DHEAS have been associated with depression (Barrett-Connor et al., 1999; Corpechot et al., 1981; Fabian et al., 2001; Goodyer et al., 1996, 2000; Takebayashi et al., 1998; Michael et al., 2000). Further, DHEAS has anxiolytic, anti-convulsant and sedative-hypnotic actions (Zinder and Dar, 1999). DHEAS is a ''neurosteroid'' and as such is synthesized in the central nervous system *de novo* (Baulieu, 1981; Majewska, 1995). Increases in synaptic concentrations of DHEAS inhibit neuronal GABA-induced currents and results in excitatory neurotransmission (Kroboth et al., 1999; Debonnel et al., 1996). Modulation of neurotransmission is related to brain function, which in turn contributes to different neuropsychological states (Majewska, 2002).

DHEAS concentrations rise throughout childhood and peak in early adulthood followed by an age-dependent decline (Rainey and Nakamura, 2008). The lowest concentrations of DHEAS occur between the ages of 65—70, pointing the possible relevance of these hormones in age-related illness (Maninger et al., 2009). Few studies have tested associations between genes related to DHEAS/DHEA function and disease. Further, of the studies testing the relationships between genes related to DHEAS concentrations and disease, no significant associations have been reported (Boger-Megiddo et al., 2008; Karlson et al., 2009). This may be due to an incomplete understanding of the relative importance of the role of genetic and environmental effects on diurnal regulation of DHEAS concentrations, particularly in aging adults.

Genetic epidemiology of DHEAS production

To date, seven family studies have estimated the impact of genetic and environmental factors on DHEAS (Table 1). The family study design takes advantage of the familial correlations between individuals across generations (i.e.: parent—child, siblings, spouses, and grandparent—grandchild) to estimate the degree to which a trait is due to familial aggregation, which includes additive genetic effects and those due to the shared (family) environment. In the absence of additional information, nuclear family data and sibling-only samples are unable to resolve familial resemblance into genetic and environmental effects since family members share both genetic and familial environments (Kendler and Neale, 2009; Rice and Borecki, 2001). Consequently, heritability estimates from these types of studies refer to the maximal effect of genes on a trait, also known as maximal heritability. One nuclear family study of 184 families reported an average heritability of 66% in families of African American descent and 58% in families of European American descent for baseline DHEAS concentrations (An et al., 2001). Another study of 348 families, reported a pooled, maximal heritability of 45% for DHEAS concentrations, unadjusted for sex differences. Maximal heritability estimates were found to differ by gender in this sample, with estimates of 29% and 74% in men and women, respectively (Rice et al., 1993). A study