Published in final edited form as:
Neuropsychology. 2013 May ; 27(3): 356–363. doi:10.1037/a0032230.

Association of Serum Dehydroepiandrosterone Sulfate and Cognition in Older Adults: Sex Steroid, Inflammatory, and Metabolic Mechanisms

Kerry L. Hildreth,
Department of Medicine, University of Colorado School of Medicine

Wendolyn S. Gozansky,
Kaiser Permanente, Denver, Colorado

Catherine M. Jankowski,
Department of Medicine, University of Colorado School of Medicine, and University of Colorado College of Nursing

Jim Grigsby,
Department of Medicine, University of Colorado School of Medicine

Pamela Wolfe, and
Colorado Biostatistical Consortium, University of Colorado School of Public Health

Wendy M. Kohrt
Department of Medicine, University of Colorado School of Medicine.

Abstract

Objective—Dehydroepiandrosterone sulfate (DHEAS) levels and cognitive function decline with age, and a role for DHEAS in supporting cognition has been proposed. Higher DHEAS levels may be associated with better cognitive performance, although potential mechanisms for this relationship are not well established.

Method—We performed a cross-sectional study of the relationship between serum DHEAS and three aspects of cognition—executive function, working memory, and processing speed—in 49 men and 54 women, aged 60–88 years, with low serum DHEAS levels. We examined three potential mechanisms of DHEAS action—sex hormone sufficiency, inflammatory status, and glucose regulation.

Results—After adjustment for multiple covariates, higher serum DHEAS levels were associated with better working memory (standardized beta coefficient 0.50, $p < .05$), with a trend toward better executive function (standardized beta coefficient 0.37, $p < .10$) in men only. There was a nonsignificant trend toward a negative association between levels of tumor necrosis factor α

Correspondence concerning this article should be addressed to Kerry L. Hildreth, MD, Division of Geriatric Medicine, University of Colorado School of Medicine, Mail Stop B-179, 12631 East 17th Avenue, Room 8111, Aurora, CO 80045. kerry.hildreth@ucdenver.edu.

(TNFα) and working memory in the combined population (standardized beta coefficient −0.22, $p < .10$). None of the glucoregulatory measures was associated with cognitive function.

Conclusions—The relationship between DHEAS and cognition is complex and differs by sex and cognitive domain. This study supports the need for further investigations of the sex-specific effects of DHEAS on cognition and its underlying mechanisms of action.

Keywords

dehydroepiandrosterone; DHEAS; cognition; aging; executive function

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are steroids second only to cholesterol in abundance in the circulation in humans (Watson, Huls, Araghinikuam, & Chung, 1996). Synthesized from pregnenolone, DHEAS can subsequently be converted into the androgens testosterone and androstenedione, which in turn can be metabolized into estrogens. The biological effects of DHEAS are unclear. The marked decline in DHEAS levels with aging (Labrie, Belanger, Cusan, Gomez, & Candas, 1997) has led to speculation that it may have a role in supporting cognitive function, which also declines with age (Salthouse, 1996).

Although the majority of DHEAS is synthesized in the adrenal cortex, this steroid is also produced in neurons and glial cells, primarily astrocytes (Benarroch, 2007). As a neurosteroid, DHEAS has been shown to interact with several receptors important in learning, memory, motor function, and behavior (Benarroch, 2007; Wigström & Gustafsson, 1985). Low levels of DHEAS have been reported in the cerebrospinal fluid and plasma of patients with Alzheimer's disease (AD; Genedani et al., 2004), and experimental models of AD have demonstrated neuroprotective effects of DHEAS derivatives in vivo (Dudas, Hanin, Rose, & Wulfert, 2004).

The mechanisms for the purported effects of DHEAS on cognition are unknown. Previous studies have demonstrated different effects of DHEAS in men compared with women with respect to cardiovascular disease (Tchernof & Labrie, 2004), suggesting an indirect mechanism of action via conversion to sex hormones. DHEAS has also been implicated in the immune dysregulation associated with aging. Low DHEAS levels have been associated with elevated levels of inflammatory cytokines, which in turn have been linked to cognitive decline (Weaver et al., 2002). Declining DHEAS levels with age may thus shift the immunologic milieu toward an increased production of proinflammatory cytokines, resulting in CNS inflammation and ultimately neurodegeneration. DHEAS levels have also been in versely related to glucose and insulin concentrations (Haffner, Valdez, Mykkanen, Stern, & Katz, 1994). Hyperglycemia (Cukierman, Gerstein, & Williamson, 2005) and hyperinsulinema (Luchsinger, Tang, Shea, & Mayeux, 2004) have been associated with cognitive impairment, thus attenuation of the neuroprotective properties may be another potential mechanism for the effect of DHEAS on cognition.

Previous studies of DHEAS and cognition have been mixed, and to our knowledge have not examined potential mechanisms. We report here results of a cross-sectional study of serum DHEAS levels and cognition in a sample of healthy older adults. We selected three

cognitive domains a priori—executive function, working memory, and processing speed—based on previous studies, suggesting these abilities may be influenced by DHEAS (Barrett-Connor & Edelstein, 1994; Berr, Lafont, Debuire, Dart-igues, & Baulieu, 1996; Davis et al., 2008). In addition, these are closely related areas of cognitive functioning, often impaired in association with a nonspecific response to a wide range of conditions affecting the central nervous system. We then extended previous research by exploring potential mechanisms for the effect of DHEAS on cognition by examining the association of sex hormones, inflammatory markers, and glucose tolerance with the cognitive outcomes of interest.

Method

Study Participants

This was a cross-sectional study of baseline (prerandomization) data from a placebo-controlled, double-blinded clinical trial of changes in bone mineral density and body composition in response to DHEAS replacement therapy reported previously (Jankowski et al., 2006). Briefly, participants were women (n = 70) and men (n = 70) aged 60+ years, with low serum DHEAS (<3.8 μmol/L, 140 μg/dL). All subjects had a medical history and screening tests to determine eligibility. Exclusion criteria included unstable health, contraindications to sex hormone therapy, use of prescribed or over-the-counter hormone therapies or oral glucocorticoids in the previous six months, cognitive impairment (Mini-Mental State Exam [MMSE] ≤ 24), (Folstein, Folstein, & McHugh, 1975), or depression (Geriatric Depression Scale score <20) (Yesavage, Brink, & Rose, 1982–1983). Use of antidepressant medications, alcohol use, and level of education were ascertained via self-administered questionnaire. Self-reported quality of life was measured by the Medical Outcomes Study Short Form 36, and we report the General Health subscale of this instrument (SFGH). The Similarities Subtest of the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997), a measure of general verbal comprehension, was used to control for differences in verbal intelligence. Verbal intelligence is positively associated with a number of mental and physical health outcomes (Gottfredson & Deary, 2004). Moreover, overall cognition (as can be measured by verbal IQ or the Similarities subtest) is highly likely to influence the majority of cognitive outcomes, as verbal IQ is strongly correlated with working memory and executive functioning. The Similarities Subtest is a 19-item test with scores ranging from 0–33. The test is relatively independent of memory and correlates well (~0.75) with the Wechsler verbal IQ score. The study was approved by the Colorado Multiple Institutional Review Board. Written informed consent was obtained from all volunteers.

Procedures

Cognitive tests—Cognitive tests were administered to subjects individually by 1 of 3 trained research personnel in one session of approximately 60 minutes duration. The tests were administered in a standardized order, using scripted instructions, in a private clinic room located in the Clinical Translational Research Center (CTRC). Cognitive testing occurred on a separate day from the other procedures.

The cognitive tests are summarized in Table 1. The primary measure of executive function was the Behavioral Dyscontrol Scale (BDS). The BDS is a 9-item, 27-point scale assessing the control of movement that is sensitive to lesions of the prefrontal cortex (Grigsby & Kaye, 1996). The BDS has been validated as a measure of executive functioning, which is the ability to regulate purposeful, goal-directed activity, and to engage in complex behavior such as activities of daily living (Grigsby & Kaye, 1996). Seven of the items involve the performance of various motor tasks with the hands, one involves working memory and attentional control, and the final item is a measure of the subject's ability to assess the accuracy of her or his performance (insight). A score of ≤14 is associated with behavioral disorders that are consistent with impaired executive cognitive function (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998). The secondary measure of executive function was the Stroop Color-Word Interference Test, which involves the inhibition of an essentially automatic response for one that requires more effort (Spreen & Strauss, 1998). The score was the number of correct responses given in 45 seconds.

The Letter-Number Sequencing Test, the primary measure of working memory, is a subtest of the WAIS-III (Wechsler, 1997). Scores were the number of correct letter and number sequences recalled. Secondary measures of working memory were Baddeley's Grammatical Reasoning Test and Luria's Word Learning Test (Christensen, 1979; Luria, 1980). The score for the Grammatical Reasoning Test was the number of correct answers. The score for Luria's Test was the number of words recalled from a list of 10 after the first trial.

The written portion of the Symbol Digit Modalities Test and Trail Making parts A and B (Trail A, Trail B) were the primary and secondary measures of processing speed, respectively (Reitan, 1958; War Department, 1944). The Symbol Digit score was the number of correct responses in 90 seconds. For Trails A and B, the score was the time in seconds required for completion of each task; lower scores indicated better (faster) performance.

DHEA, sex hormones, and cytokines—Serum samples were obtained between 7:00 and 9:00 a.m. after an overnight fast. DHEAS, total testosterone (T), total estradiol (E_2), and sex-hormone binding globulin (SHBG) were measured as described previously (Jankowski et al., 2006). Sex hormones, IL-6 and TNFα concentrations were measured by ELISA (R&D Systems, Minneapolis, MN). Intra- and interassay CVs were 5.2% and 11.0% for IL-6, and 5.4% and 7.1% for TNFα.

Oral glucose tolerance test (OGTT)—Subjects were instructed to eat a weight-maintaining diet containing at least 150 g of carbohydrate per day for three days before the OGTT. The 75-g OGTTs were performed in the morning after an overnight fast. Blood samples were obtained before and 30, 60, 90, and 120 minutes after glucose ingestion for plasma glucose and insulin determinations. The total areas under the glucose curve (GLU_{AUC}) and insulin curve (INS_{AUC}) were calculated using the trapezoidal rule.

Statistical Analyses

We hypothesized that higher serum DHEAS levels would be associated with better cognitive function. Furthermore, we examined three mechanistic models underlying cognitive

function: (1) sex hormone sufficiency (DHEAS, T, and E_2); (2) inflammatory state (TNFα, and IL-6); and (3) metabolic function (fasting glucose, fasting insulin, GLU_{AUC}, and INS_{AUC}). Age, education, alcohol use, antidepressant use, SFGH, Similarities Subtest score, and test administrator were considered as covariates. The primary and secondary cognitive measures were examined for skewness and a linear relationship with the continuous explanatory variables. Trails A and B times were log transformed for analysis. Sex differences were evaluated by two-sample *t* tests.

Correlations of mechanistic variables and covariates with the BDS, Letter-Number Sequencing, and Symbol Digit tests were estimated bivariately; covariates were excluded from further consideration if the Pearson's product-moment correlation coefficient was less than 0.15 in any pairwise test. The association of BDS, Letter-Number Sequencing, and Symbol Digit tests with sex hormones, inflammatory markers, and metabolic markers was tested in separate least squares regression models. The sex hormone sufficiency models were estimated separately for men and women because of sex differences in serum DHEAS and sex hormones. Standardized beta coefficients were estimated by regressing each dependent variable first on each group of mechanistic variables (Model 1) and after adjusting for the selected covariates (Model 2). No adjustments were made for multiple comparisons or endpoints. A two-sided p value <0.05 was used to define statistical significance. Statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC).

Results

Demographics

Two hundred sixty-one volunteers were assessed for eligibility. Of these, 11 men and two women had serum DHEAS levels that exceeded the inclusion criteria. Seventy men and 70 women were enrolled in the larger study. Forty-nine men and 54 women completed the cognitive testing and were included in this analysis. Subjects who completed the cognitive testing completed fewer years of education than subjects who did not complete cognitive testing (82.8% vs. 97.2%, $p = .01$) but did not otherwise differ from the included subjects (data not shown). With the exception of alcohol use, there were no sex-specific differences in demographic variables, self-reported general health, or depression (see Table 2). Men scored significantly lower on the MMSE and higher on the Similarities Subtest of verbal intelligence. Hormone levels reflected expected sex differences; average serum DHEAS levels were approximately 15% of the levels reported for young women (median 324 μg/dl) and men (median 420 μg/dl) (Villareal, Holloszy, & Kohrt, 2000).

Cognition

There were no significant differences between men and women in any of the cognitive outcome measures (see Table 2).

Sex Hormone Sufficiency and Cognition

The relationship of DHEAS, T, and E_2 with cognition differed for women and men (see Table 3). In women, serum DHEAS levels were positively correlated with both the BDS and Letter-Number Sequencing in the unadjusted model ($r = .49$ and 0.36), however, neither

correlation remained significant after adjusting for covariates. E_2 was negatively correlated with Letter-Number Sequencing in women in the unadjusted, but not the adjusted model (r = −0.38 and −0.24). Post hoc linear regression analysis of E_2 on secondary measures of working memory (Grammatical Reasoning and Luria Word Learning) was consistent with the primary measure. Standardized beta coefficients of −0.31 and −0.32, and p values just short of statistical significance (p = .09 and 0.06, respectively) were observed in the unadjusted model, but no significant associations were observed in the adjusted models.

Serum DHEAS was also positively correlated with the BDS and Letter-Number Sequencing in men. The strength of the correlation with the BDS increased after adjusting for covariates, but did not reach statistical significance. Analysis of DHEAS on the secondary measure of executive function, the Stroop Test, was consistent with the BDS, that is, there was a significant positive correlation in the unadjusted model which was lost after adjusting for covariates (data not shown). In contrast to the results in women, the association of DHEAS with Letter-Number Sequencing was significant after adjusting for covariates. However, neither secondary measure of working memory showed a similar pattern (data not shown).

With the exception of the negative correlation between E_2 and Letter-Number Sequencing in women, there were no significant correlations between E_2 or T and any of the primary cognitive measures. We found no significant correlation between DHEAS, E_2, or T and the Symbol Digit Test in either model in women or men. Substituting free E_2 and T in the sex hormone models did not appreciably change the results (data not shown).

Inflammatory State and Cognition

Serum TNFα and IL-6 levels were 2.0 ± 1.6 pg/mL, and 2.4 ± 3.5 pg/mL, respectively (mean ± *SD*). Because levels of these cytokines did not differ significantly between women and men, regression models included the total sample (see Table 4). TNFα was positively correlated with the BDS in the adjusted model. TNFα was not correlated with performance on the Stroop test (data not shown).

We found a negative correlation between TNFα and Letter-Number Sequencing in the unadjusted model; the strength and direction of the correlation persisted after adjusting for covariates, but did not remain statistically significant. We obtained a similar result with the Grammatical Reasoning Test (standardized beta coefficient −0.23, p = .02 unadjusted; −0.16, p = .14 adjusted). TNFα was not significantly correlated with performance on the Luria Word Learning Test (data not shown).

There was a weak negative association between TNFα and the Symbol Digit Test in the unadjusted model, which did not persist after adding the covariates. We found no significant correlations between IL-6 and any of the cognitive measures.

Metabolic Function and Cognition

Fasting serum glucose and insulin levels were 91.1 ± 10.3 mg/dL and 7.4 ± 3.7 μIU/mL, respectively (mean ± *SD*). Areas under the curve were $172 \pm 37 \times 10^{-2}$ mg/dL/min for glucose and $6.3 \pm 3.5 \times 10^{-2}$ μU/mL/min for insulin. After univariate analysis, only GLU_{AUC} and INS_{AUC} remained in the final models (see Table 5). INS_{AUC} was positively

correlated with the Symbol Digit Test in the unadjusted model, but not after adjustment for covariates. We found no other significant correlations between metabolic function and cognition in either the unadjusted or adjusted models.

In summary, in unadjusted models, higher serum DHEAS levels were associated with better executive cognitive functioning, and a trend toward better working memory. After adjusting for covariates, however, significant positive associations were only found between DHEAS and working memory in men, and between TNFα and executive function. None of the metabolic parameters was significantly associated with cognitive function.

Discussion

In this cross-sectional study, the associations of serum DHEAS levels and cognition were sex-specific, limited to working memory, and were not explained by conversion of DHEAS to other sex hormones or via proinflammatory or glucoregulatory mechanisms. The correlation of the cognitive variables with such covariates as age and education, and the relationship between DHEAS and age strongly influenced the association of DHEAS with executive cognitive function and word processing speed, as measured by the BDS and Letter-Number Sequencing, respectively.

Sex differences are likely to play a major role in any effects of DHEAS on cognition as a result of its extensive metabolism to androgens and estrogens. Studying combined populations of men and women, and/or failing to adjust for levels of other sex hormones, may obscure subtle relationships and explain some of the mixed findings among studies. In combined populations, the InCHIANTI cohort study demonstrated a significant positive association between baseline serum DHEAS levels and MMSE score (Valenti et al., 2009), whereas the population-based Rotterdam study did not (Kalmijn et al., 1998). The Rancho Bernardo and PAQUID studies found that DHEAS levels were positively correlated with cognitive measures, but only in women (Barrett-Connor & Edelstein, 1994; Berr et al., 1996).

Studies of women only or men only have also yielded mixed findings. Our results are consistent with those of Yaffe et al., who found no association between DHEAS levels and multiple tests of cognition in older women (Yaffe et al., 1998). However, a recent study of older Australian women found that higher serum DHEAS levels were associated with better executive function, working memory, and concentration (Davis et al., 2008). With the exception of better working memory performance, our findings in men generally support both the Baltimore Longitudinal Study of Aging and the Massachusetts Male Aging Study, neither of which detected significant associations between DHEAS levels and cognitive function (Fonda, Bertrand, O'Donnell, Longcope, & McKinlay, 2005; Moffat et al., 2000).

The changing hormonal milieu that occurs with aging may obscure associations between DHEAS and cognition, although few other studies have adjusted for levels of other sex hormones. Although we cannot account for the conversion of DHEAS to estrogens or androgens, we found no evidence for independent effects of estrogen or testosterone on cognition. This finding is consistent with previous studies, including the Massachusetts Male

Aging Study, in which no association of testosterone or estrone with cognition was observed (Fonda et al., 2005). Similarly, adjustment for total testosterone and estradiol in the InCHIANTI study had no effect on the observed relationship between DHEAS and MMSE score (Valenti et al., 2009). The complex interrelationships between DHEAS, androgens, and estrogens, and the hormonal changes associated with aging, preclude ruling out a role for other sex hormones. For example, although DHEAS levels are well known to decrease with age, recent examination of data from the Study of Women Across the Nation (SWAN) demonstrated an *increase* in DHEAS levels during the menopausal transition (Crawford et al., 2009). It may, therefore, be important to consider ovarian status in addition to androgen and estrogen levels when examining the effects of DHEAS.

Inflammation

Numerous inflammatory diseases that typically present at older ages, including Alzheimer's disease (Yanase et al., 1996), rheumatoid arthritis (Sambrook, Eisman, Champion, & Pocock, 1988), and atherosclerotic cardiovascular disease (Barrett-Connor & Goodman-Gruen, 1995), have been associated with low levels of serum DHEAS. This has led to speculation about the relation between the age-related decline in DHEAS and the coincident dysregulation of the immune system. Animal and human studies have demonstrated an inhibitory effect of DHEAS on the release of inflammatory cytokines, including IL-6 and TNFα (Daynes et al., 1993; James et al., 1997; Kimura et al., 1998; Young, Skibinski, Mason, & James, 1999). TNFα inhibits the enzyme 17-α-hydroxylase, which converts 17-α-hydroxypregnenolone to DHEA, and downregulates mRNA expression of DHEA sulfotransferase, which converts DHEA to DHEAS (Herrmann, Scholmerich, & Straub, 2002). Declining levels of DHEAS with age may therefore lead to a permissive increase in circulating inflammatory cytokines, which may in turn depress DHEAS levels.

In the MacArthur Foundation Program in Successful Aging, high levels of IL-6 were associated with lower baseline cognitive functioning and subsequent decline (Weaver et al., 2002). Furthermore, a negative association between TNFα levels and MMSE scores has been observed in patients with myotonic dystrophy, a disorder characterized by a proinflammatory state and low DHEAS levels (Johansson et al., 2000). In the present study, there was a positive association of TNFα with executive function; however, this association was strongly influenced by covariates, thus we hesitate to endorse an inflammatory mechanism underpinning cognitive function in our healthy population. Furthermore, we found no significant associations between IL-6 and any cognitive measures. Notably, there were no subjects with TNFα or IL-6 levels outside of the reference ranges, which may have limited our ability to detect significant associations between inflammatory state and cognition.

Metabolic Function

A growing body of evidence supports a critical role for insulin in cognitive function, and numerous studies have demonstrated an increased risk of cognitive impairment associated with both diabetes and insulin resistance (Cukierman et al., 2005; Luchsinger et al., 2004). We found no relation between insulin or glucose AUC and any of our cognitive measures. This may reflect the general good health of our study population, which had glucose

tolerance and insulin sensitivity within normal ranges, and just two participants on antihyperglycemic medications.

Findings from this study suggest mechanisms other than those studied here may explain the beneficial effects of DHEAS on cognition that have been observed. In animal studies, DHEAS appears to act as an excitatory neurosteroid in the CNS through antagonistic effects on the GABA-receptor (Majewska, 1992) and agonist effects on the sigma-receptor (Monnet, Mahe, Robel, & Baulieu, 1995). Both GABA antagonists and sigma agonists have been shown to enhance memory in animals and humans (Wolf & Kirschbaum, 1999). DHEAS is known to have antiglucocorticoid activity (Kalimi, Shafagoj, Loria, Padgett, & Regelson, 1994), leading some to speculate that alterations in the balance between DHEAS and glucocorticoids, which modulate mood and cognition, may contribute to psychiatric and cognitive disorders (Hechter, Grossman, & Chatterton, 1997). These neurobiological effects may be in part responsible for the anxiolytic and antidepressant properties of DHEAS (Wolf & Kirschbaum, 1999), which could also potentially affect cognitive function.

Strengths and Limitations

Our study was based on data collected in the setting of a randomized controlled clinical trial. Thus, although the sample size was moderate, the rigorous trial design allowed us to take the novel approach of evaluating three potential mechanisms (sex hormones, inflammation, and glucoregulation) to explain the relation of DHEAS to cognition. Instead of measuring "general" cognitive function, we specifically selected three cognitive domains of interest (executive function, working memory, and processing speed) and included multiple measures within each domain to allow us to evaluate the consistency of the relationships. In addition to age and education, we adjusted for multiple potential confounders of cognitive function including self-reported quality of life, verbal intelligence, and test administrator.

This study had certain limitations that may have affected the results and their interpretation. First, we relied upon a single blood draw for measures of DHEAS, TNFα, and IL-6. Although DHEAS varies significantly *between* individuals, intraindividual variability is minimal (Thomas et al., 1994). Because both the sex hormones (testosterone and estradiol) and inflammatory markers (TNFα and IL-6) exhibit diurnal variation (Petrovsky, McNair, & Harrison, 1998), samples were drawn consistently between 7:00 and 9:00 a.m. for all subjects to minimize this effect. Second, we did not measure cortisol levels in this study. Cortisol and DHEA share the same steroid precursors (Herrmann et al., 2002), and hypothalamic-pituitary axis dysfunction, elevated cortisol levels, and the ratio of free cortisol to DHEAS have been linked to cognitive impairment and dementia (Kalmijn et al., 1998; Lupien et al., 1994; Seeman, McEwen, Singer, Albert, & Rowe, 1997). Third, cognitive testing was performed by three different administrators. This unforeseen circumstance led us to include test administrator as a covariate. Finally, subjects were selected to have low DHEAS levels, which may limit the generalizability of our findings. However, very few subjects (11 men and 2 women of 261 screened) were excluded from the study for DHEAS levels, exceeding the inclusion cut-off. Further, the mean DHEAS levels for both men and women in this study were within usual ranges reported for this age group

(Guber, Farag, Lo, & Sharp, 2006). Subjects were also healthy and cognitively intact, thus it is unclear whether similar findings would be observed in other populations.

Conclusion

The link between DHEAS and cognition remains intriguing and unanswered. The heterogeneity of the literature may reflect complex interactions between DHEAS, sex and HPA-axis hormones, inflammatory cytokines, insulin, and other factors, compounded by potentially different effects on specific domains of cognitive function. Findings from this exploratory study suggest that sex hormones, inflammation, and glucoregulation are not likely mechanisms for effects of DHEAS on cognitive function, and further study into the modest associations we found is required. Future research may need to examine multiple factors in concert, as opposed to looking for a significant effect on cognition attributable to a single factor. Considering that DHEAS supplements are widely available, easily administered, inexpensive, and have apparently negligible side effects, replacing DHEAS in persons with low levels would be an attractive option if beneficial effects on cognition could be demonstrated. However, a systematic review of controlled trials does not currently support the use of DHEAS for cognitive function (Grimley, Malouf, Huppert, & van Niekerk, 2006). High quality, randomized controlled trials of sufficient duration are needed to better understand the effects and potential mechanisms of DHEAS on cognitive performance.

Acknowledgments

This study was supported by a National Institutes of Health (NIH) Grant 1R01AG18857 (WMK) and by NIH/NCATS Colorado CTSI Grant Number UL1 TR000154. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

We thank Kathryn Kaye, PsyD for contributing her expertise regarding cognitive testing.

References

Barrett-Connor E, Edelstein SL. A prospective study of dehydroepiandrosterone sulfate and cognitive function in an older population: The Rancho Bernardo Study. Journal of the American Geriatrics Society. 1994; 42:420–423. [PubMed: 8144828]

Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. Annals of the New York Academy of Sciences. 1995; 774:259–270. doi:10.1111/j.1749-6632.1995.tb17386.x-i1. [PubMed: 8597464]

Benarroch EE. Neurosteroids: Endogenous modulators of neuronal excitability and plasticity. Neurology. 2007; 68:945–947. doi:10.1212/01.wnl.0000257836.09570.e1. [PubMed: 17372131]

Berr C, Lafont S, Debuire B, Dartigues JF, Baulieu EE. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: A French community-based study. Proceedings of the National Academies of Science of the United States of America. 1996; 93:13410–13415. doi:10.1073/pnas.93.23.13410.

Christensen, AL. Luria's neuropsychological investigation (Vol. 2). Munksgaard; Copenhagen, Denmark: 1979.

Crawford S, Santoro N, Laughlin GA, Sowers MF, McConnell D, Sutton-Tyrrell K, Lasley B. Circulating dehydroepiandrosterone sulfate concentrations during the menopausal transition. Journal of Clinical Endocrinology and Metabolism. 2009; 94:2495–2951. doi:10.1210/jc.2009-0386. [PubMed: 19401368]

Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes–systematic overview of prospective observational studies. Diabetologia. 2005; 48:2460–2469. doi:10.1007/s00125-005-0023-4. [PubMed: 16283246]

Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ. Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. Journal of Clinical Endocrinology and Metabolism. 2008; 93:801–808. doi:10.1210/jc.2007-2128. [PubMed: 18073302]

Daynes RA, Araneo BA, Ershler WB, Maloney C, Li GZ, Ryu SY. Altered regulation of IL-6 production with normal aging. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfated derivative. Journal of Immunology. 1993; 150:5219–5230.

Dudas B, Hanin I, Rose M, Wulfert E. Protection against inflammatory neurodegeneration and glial cell death by 7beta-hydroxy epiandrosterone, a novel neurosteroid. Neurobiology of Disease. 2004; 15:262–268. doi:10.1016/j.nbd.2003.11.001. [PubMed: 15006696]

Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. doi: 10.1016/0022-3956(75)90026-6. [PubMed: 1202204]

Fonda SJ, Bertrand R, O'Donnell A, Longcope C, McKinlay JB. Age, hormones, and cognitive functioning among middle-aged and elderly men: Cross-sectional evidence from the Massachusetts Male Aging Study. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2005; 60:385–390. doi:10.1093/gerona/60.3.385.

Genedani S, Rasio G, Cortelli P, Antonelli F, Guidolin D, Galantucci M, Agnati LF. Studies on homocysteine and dehydroepiandrosterone sulphate plasma levels in Alzheimer's disease patients and in Parkinson's disease patients. Neurotoxicity Research. 2004; 6:327–332. doi:10.1007/BF03033443. [PubMed: 15545016]

Gottfredson LS, Deary IJ. Intelligence predicts health and longevity, but why? Current Directions in Psychological Science. 2004; 13:1–4. doi:10.1111/j.0963-7214.2004.01301001.x.

Grigsby, J.; Kaye, K. Behavioral Dyscontrol Scale: Manual (Vol. 2). Ward, CO.: 1996.

Grigsby J, Kaye K, Baxter J, Shetterly SM, Hamman RF. Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. Journal of the American Geriatrics Society. 1998; 46:590–596. [PubMed: 9588372]

Grimley EJ, Malouf R, Huppert F, van Niekerk JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. Cochrane Database of Systematic Reviews. 2006; 4:CD006221. [PubMed: 17054283]

Guber, HA.; Farag, AF.; Lo, J.; Sharp, J. Evaluation of endocrine function.. In: McPherson, RA.; Pincus, MR., editors. Henry's clinical diagnosis and management by laboratory methods. 21st ed.. W. B. Saunders Company; Philadelphia, PA: 2006.

Haffner SM, Valdez RA, Mykkanen L, Stern MP, Katz MS. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. Metabolism: Clinical and Experimental. 1994; 43:599–603. doi:10.1016/0026-0495(94)90202-X. [PubMed: 8177048]

Hechter O, Grossman A, Chatterton RT Jr. Relationship of dehydroepiandrosterone and cortisol in disease. Medical Hypotheses. 1997; 49:85–91. doi:10.1016/S0306-9877(97)90258-9. [PubMed: 9247914]

Herrmann M, Scholmerich J, Straub RH. Influence of cytokines and growth factors on distinct steroidogenic enzymes in vitro: A short tabular data collection. Annals of the New York Academy of Sciences. 2002; 966:166–186. doi:10.1111/j.1749-6632.2002.tb04213.x. [PubMed: 12114270]

James K, Premchand N, Skibinska A, Skibinski G, Nicol M, Mason JI. IL-6, DHEA and the ageing process. Mechanisms of Ageing and Development. 1997; 93:15–24. doi:10.1016/S0047-6374(96)01807-6. [PubMed: 9089567]

Jankowski CM, Gozansky WS, Schwartz RS, Dahl DJ, Kittelson JM, Scott SM, Kohrt WM. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: A randomized, controlled trial. Journal of Clinical Endocrinology and Metabolism. 2006; 91:2986–2993. doi:10.1210/jc.2005-2484. [PubMed: 16735495]

Johansson A, Carlstrom K, Ahren B, Cederquist K, Krylborg E, Forsberg H, Olsson T. Abnormal cytokine and adrenocortical hormone regulation in myotonic dystrophy. Journal of Clinical Endocrinology and Metabolism. 2000; 85:3169–3176. doi:10.1210/jc.85.9.3169. [PubMed: 10999804]

Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). [Review]. Molecular and Cellular Biochemistry. 1994; 131:99–104. doi:10.1007/BF00925945. [PubMed: 8035785]

Kalmijn S, Launer LJ, Stolk RP, de Jong FH, Pols HA, Hofman A, Lamberts SW. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. Journal of Clinical Endocrinology and Metabolism. 1998; 83:3487–3492. doi:10.1210/jc.83.10.3487. [PubMed: 9768651]

Kimura M, Tanaka S, Yamada Y, Kiuchi Y, Yamakawa T, Sekihara H. Dehydroepiandrosterone decreases serum tumor necrosis factor-alpha and restores insulin sensitivity: Independent effect from secondary weight reduction in genetically obese Zucker fatty rats. Endocrinology. 1998; 139:3249–3253. doi:10.1210/en.139.7.3249. [PubMed: 9645700]

Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. Journal of Clinical Endocrinology and Metabolism. 1997; 82:2396–2402. doi: 10.1210/jc.82.8.2396. [PubMed: 9253307]

Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology. 2004; 63:1187–1192. doi:10.1212/01.WNL.0000140292.04932.87. [PubMed: 15477536]

Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ. Basal cortisol levels and cognitive deficits in human aging. The Journal of Neuroscience. 1994; 14:2893–2903. [PubMed: 8182446]

Luria, AR. Higher cortical functions in man (Vol. 2). Basic Books; New York, NY: 1980. doi: 10.1007/978-1-4615-8579-4

Majewska MD. Neurosteroids: Endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. [Review]. Progress in Neurobiology. 1992; 38:379–394. doi:10.1016/0301-0082(92)90025-A. [PubMed: 1349441]

Moffat SD, Zonderman AB, Harman SM, Blackman MR, Kawas C, Resnick SM. The relationship between longitudinal declines in dehydroepiandrosterone sulfate concentrations and cognitive performance in older men. Archives of Internal Medicine. 2000; 160:2193–2198. doi:10.1001/archinte.160.14.2193. [PubMed: 10904463]

Monnet FP, Mahe V, Robel P, Baulieu EE. Neurosteroids, via sigma receptors, modulate the [3H]norepinephrine release evoked by N-methyl-D-aspartate in the rat hippocampus. Proceedings of the National Academy of Sciences of the United States of America. 1995; 92:3774–3778. doi: 10.1073/pnas.92.9.3774. [PubMed: 7731982]

Petrovsky N, McNair P, Harrison LC. Diurnal rhythms of pro-inflammatory cytokines: Regulation by plasma cortisol and therapeutic implications. Cytokine. 1998; 10:307–312. doi:10.1006/cyto.1997.0289. [PubMed: 9617577]

Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and Motor Skills. 1958; 8:271–276.

Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychological Review. 1996; 103:403–428. doi:10.1037/0033-295X.103.3.403. [PubMed: 8759042]

Sambrook PN, Eisman JA, Champion GD, Pocock NA. Sex hormone status and osteoporosis in postmenopausal women with rheumatoid arthritis. Arthritis and Rheumatism. 1988; 31:973–978. doi: 10.1002/art.1780310805. [PubMed: 2970263]

Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. Journal of Clinical Endocrinology and Metabolism. 1997; 82:2458–2465. doi:10.1210/jc.82.8.2458. [PubMed: 9253318]

Spreen, O.; Strauss, E. A compendium of neuropsychological tests: Administration, norms and commentary. Oxford University Press; New York, NY: 1998.

Tchernof A, Labrie F. Dehydroepiandrosterone, obesity and cardiovascular disease risk: A review of human studies. European Journal of Endocrinology. 2004; 151:1–14. doi:10.1530/eje.0.1510001. [PubMed: 15248817]

Thomas G, Frenoy N, Legrain S, Sebag-Lanoe R, Baulieu EE, Debuire B. Serum dehydroepiandrosterone sulfate levels as an individual marker. Journal of Clinical Endocrinology and Metabolism. 1994; 79:1273–1276. doi:10.1210/jc.79.5.1273. [PubMed: 7962319]

Valenti G, Ferrucci L, Lauretani F, Ceresini G, Bandinelli S, Luci M, Schwartz RS. Dehydroepiandrosterone sulfate and cognitive function in the elderly: The InCHIANTI Study. Journal of Endocrinology. Invest. 2009; 32:766–772. doi:10.3275/6438.

Villareal DT, Holloszy JO, Kohrt WM. Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. Clinical Endocrinology (Oxford). 2000; 53:561–568. doi: 10.1046/j.1365-2265.2000.01131.x. [PubMed: 11106916]

War Department. Trail Making Test manual of directions and scoring. Adjutant General's Office; Washington, DC: 1944.

Watson RR, Huls A, Araghinikuam M, Chung S. Dehydroepiandrosterone and diseases of aging. Drugs and Aging. 1996; 9:274–291. doi:10.2165/00002512-199609040-00005. [PubMed: 8894525]

Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002; 59:371–378. doi: 10.1212/WNL.59.3.371. [PubMed: 12177370]

Wechsler, D. WAIS-III Wechsler Adult Intelligence Scale. The Psychological Corporation; San Antonio, TX: 1997.

Wigström H, Gustafsson B. Facilitation of hippocampal long-lasting potentiation by GABA antagonists. Acta Physiologica Scandinavica. 1985; 125:159–172. doi:10.1111/j.1748-1716.1985.tb07703.x. [PubMed: 2996303]

Wolf OT, Kirschbaum C. Actions of dehydroepiandrosterone and its sulfate in the central nervous system: Effects on cognition and emotion in animals and humans. Brain Research Reviews. 1999; 30:264–288. doi:10.1016/S0165-0173(99)00021-1. [PubMed: 10567728]

Yaffe K, Ettinger B, Pressman A, Seeley D, Whooley M, Schaefer C, Cummings S. Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: A prospective study. Biological Psychiatry. 1998; 43:694–700. doi:10.1016/S0006-3223(97)00303-X. [PubMed: 9583004]

Yanase T, Fukahori M, Taniguchi S, Nishi Y, Sakai Y, Takayanagi R, Nawata H. Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) in Alzheimer's disease and in cerebrovascular dementia. Endocrine Journal. 1996; 43:119–123. doi:10.1507/endocrj.43.119. [PubMed: 8732462]

Yesavage JA, Brink T, Rose T. Development and validation of a geriatric depression screening scale. Journal of Psychiatric Research. 1982–1983; 17:37–49. doi:10.1016/0022-3956(82)90033-4. [PubMed: 7183759]

Young DG, Skibinski G, Mason JI, James K. The influence of age and gender on serum dehydroepiandrosterone sulphate (DHEA-S), IL-6, IL-6 soluble receptor (IL-6 sR) and transforming growth factor beta 1 (TGF-beta1) levels in normal healthy blood donors. Clinical and Experimental Immunology. 1999; 117:476–481. doi:10.1046/j.1365-2249.1999.01003.x. [PubMed: 10469050]

Table 1

Cognitive Domains and Outcome Measures

Cognitive domain	Test	Possible range
Executive Cognitive Function	Behavioral Dyscontrol Scale	0–27
	Stroop Color Word Interference Part III	0–100
Working Memory	Letter-Number Sequencing	0–21
	Grammatical Reasoning Test	0–32
	Luria Word Learning Test[a]	0–10
Information Processing Speed	Symbol Digit Modalities Test	0–110
	Trail Making PartsA&B (sec)	1–300

[a]Number of words recalled in the first trial.

Table 2

Demographics, Sex Hormones, and Cognitive Function by Sex

Variable	Women		Men		*p* value
	n	Mean ± *SD* or %	*n*	Mean ± *SD* or %	
Age	54	69.2 ± 7.1	49	69.0 ± 6.3	0.88
Antidepressant use					0.31
Never	39	81.3	41	91.1	
Throughout	8	16.7	3	6.7	
Started	1	2.1	1	2.2	
Alcohol use					0.46
None	16	29.6	0	20.4	
≤ 1–2 drinks/week	29	53.7	25	51.0	
1–2 drinks/day	8	14.8	12	24.5	
≥ 3 drinks/day	1	1.9	2	4.1	
Education > HS					0.68
No	9	18.8	7	15.6	
Yes	39	81.3	38	84.4	
SF-36 General Health Subscale	51	81.1 ± 15.0	46	79.9 ± 13.1	0.68
Geriatric Depression Scale	54	3.6 ± 3.4	49	4.2 ± 3.6	0.37
MMSE	54	28.7 ± 1.2	49	28.1 ± 1.5	0.02
WAIS- III Similarities Subset	54	25.1 ± 4.3	49	27.1 ± 3.4	0.009
DHEAS (μg/dL)	54	45.2 ± 28.5	49	64.6 ± 27.3	<0.001
Testosterone (ng/dL)	38	22.6 ± 12.0	49	399.6 ± 132.1	<0.001
Estradiol (pg/mL)	54	30.2 ± 9.6	49	47.8 ± 8.6	<0.001
Behavioral Dyscontrol Scale	54	18.3 ± 3.8	49	18.0 ± 3.1	0.69
Stroop Color Word Interference	54	38.6 ± 14.2	42	33.9 ± 10.8	0.08
Letter-Number Sequencing	54	9.7 ± 2.3	49	10.0 ± 2.7	0.66
Grammatical Reasoning Test	54	13.2 ± 6.6	49	14.3 ± 7.8	0.41
Luria Word Learning Test	54	5.6 ± 1.5	49	5.4 ± 1.4	0.66
Symbol Digit Modalities Test	54	43.9 ± 8.5	49	41.0 ± 9.9	0.12
Trails A (seconds)	54	41.5 ± 13.9	49	40.9 ± 17.6	0.85
Trails B (seconds)	54	96.2 ± 60.5	49	101.9 ± 62.2	0.63

Table 3

Standardized Beta Coefficients From Linear Regression Models for Women and Men Separately for Each Dependent Variable Entering DHEAS, T and E_2 Together (Model 1), Then in Concert With Other Covariates (Model 2)

Dependent variable	Independent variable	Women		Men	
		Model 1	Model 2	Model 1	Model 2
Behavioral	DHEAS	0.49*	0.20	0.32*	0.37†
Dyscontrol	Testosterone	0.09	0.10	–0.24	–0.20
Scale	Estradiol	–0.31	–0.30	0.01	–0.12
	Adjusted R^2	0.19	0.30	0.09	0.03
Letter-Number	DHEAS	0.36*	0.14	0.27†	0.50*
Sequencing	Testosterone	0.11	0.15	0.05	0.16
	Estradiol	–0.38*	–0.24	0.03	–0.17
	Adjusted R^2	0.12	0.07	0.02	0.45
Symbol Digit	DHEAS	0.27	–0.05	0.24†	0.21
Modalities Test	Testosterone	0.03	0.16	–0.14	–0.11
	Estradiol	–0.13	–0.13	0.28†	0.19
	Adjusted R^2	0.00	0.20	0.07	0.08

Note.

Covariates include WAIS-III Similarities Subtest, Medical Outcomes Short Form 36-General Health, Education, Age, and Test Administrator.

† $p < .10$.

* $p < .05$.

Table 4

Standardized Beta Coefficients From Linear Regression Models for Each Dependent Variable Entering TNFα and IL-6 Together (Model 1), and Then in Concert With Other Covariates (Model 2)

Dependent variable	Independent variables	Model 1	Model 2
Behavioral	TNFα	0.09	0.31*
Dyscontrol Scale	IL-6	0.07	0.06
	Adjusted R^2	0.00	0.22
Letter-Number	TNFα	–0.20*	–0.22†
Sequencing	IL-6	–0.02	–0.03
	Adjusted R^2	0.02	0.06
Symbol Digit	TNFα	–0.18†	–0.02
Modalities Test	IL-6	0.05	0.09
	Adjusted R^2	0.01	0.14

Note.

Covariates include WAIS-III Similarities Subtest, Medical Outcomes Short Form 36-General Health, Education, Age, and Test Administrator.

† $p < .10$.

* $p < .05$.

Table 5

Standardized Beta Coefficients From Linear Regression Models for Each Dependent Variable Entering Glucose and Insulin Together (Model 1), and Then in Concert With the Other Covariates (Model 2)

Dependent variable	Independent variables	Model 1	Model 2
Behavioral	Glucose AUC	0.00	0.05
Dyscontrol Scale	Insulin AUC	0.10	0.06
	Adjusted R^2	0.00	0.13
Letter-Number	Glucose AUC	–0.19†	–0.17
Sequencing	Insulin AUC	–0.01	–0.00
	Adjusted R^2	0.02	0.05
Symbol Digit	Glucose AUC	–0.11	0.00
Modalities Test	Insulin AUC	0.22*	0.09
	Adjusted R^2	0.03	0.14

Note.

Covariates include WAIS-III Similarities Subtest, Medical Outcomes Short Form 36-General Health, Education, Age, and Test Administrator.

† $p < .10$.

* $p < .05$.