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DHEA SUPPLEMENTATION AND COGNITION IN POSTMENOPAUSAL WOMEN

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Previous work has suggested that DHEA supplementation may have adverse cognitive effects in elderly women. This article analyzed 24-h measurements of DHEA, DHEAS, and cortisol to determine if cognitive decrease with treatment is mediated by DHEA's impact on endogenous cortisol. It was found that DHEA administration increased cortisol at several hours during the day. In the treatment group, cortisol was positively associated with cognition at study completion. An increase in negative associations between DHEA(S) levels and cognition was found at completion. Increased cortisol does not explain the cognitive deficits associated with DHEA, suggesting a direct negative effect of exogenous DHEA on cognition.

Keywords cognition, cortisol, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), postmenopausal, women

The neuropsychology of steroid hormones is a burgeoning area of research. Dehydroepiandrosterone (DHEA) is an adrenal androgen that declines with age (Orentreich et al., 1984; Sulcová et al., 1997). Researchers have hypothesized DHEA as a possible marker of aging and longevity (Roth et al., 2002). Because of its reported positive neural effects, including possible enhancement of cognition, DHEA supplementation has been advocated as a powerful anti-aging tool. DHEA also appears to have an agonist-antagonist relationship with the adrenal hormone cortisol in neural functioning, physical health, and cognition (Browne et al., 1993; Kalimi et al., 1994; Wolf & Kirschbaum, 1999; Ferrari et al., 2004; Marklund et al., 2004). However, a clear relationship between DHEA and cortisol, especially as they collectively impact cognition, has yet to be identified. Given the role of DHEA as a precursor to other more potent steroid hormones, its opposing relationship to cortisol, and its current use as an anti-aging supplement, a comprehensive study of its direct and indirect effects on cognition and cortisol is warranted. Of specific interest is an exploration of the effects of DHEA in a population of postmenopausal women.

Studies on DHEA supplementation and cognition in older adults have not provided consistent results (Racchi et al., 2003; Vallee et al., 2001). One study by Wolkowitz et al. (1997) showed an improvement in cognition following DHEA administration in six clinically depressed middle-aged, and elderly, patients. However, this study has a low subject number, the researchers did not control for placebo effects or for improvement in mood, and cognitive improvement was only found on a verbal memory subtest measuring automatic processing. No improvement was found on other indices of the test, such as those measuring free recall, recognition, vigilance/attention, or fluency.

Other studies showed no effect on cognition following DHEA administration (Berr et al., 1996; Burkenhäger-Gillesse et al., 1994; Yaffe et al., 1998). In a study by Wolf, Neumann, et al. (1997), no effect or detrimental effects on cognition were found following DHEA administration, despite increased levels of DHEA. The neuropsychological tests utilized in these studies included two uncited measures and did not comprehensively measure naming and visuospatial abilities, which are known to be sensitive to hormonal fluctuation (Henderson et al., 1996; Caldwell & Watson, 1952; Kampen & Sherwin, 1994; Phillips & Sherwin, 1992a, 1992b; Sherwin, 1988).

In terms of sex difference, some studies have found a link between DHEAS and cognitive function among men, but no difference among women (Mazat et al., 2001; Tilvis et al., 1999; Ravaglia et al., 2002). Contrariwise, other studies report a positive correlation between DHEAS and cognitive impairment among women (see Morrison et al., 2000). In another study, Kratz et al. (1999, 2000) found detrimental effects of DHEA supplementation in several cognitive domains for menopausal women. Yet Kratz utilized a single hormonal sample to evaluate cognition at baseline and study completion, and failed to examine the impact of DHEA on plasma cortisol levels.

In a study attempting to explain DHEA's complex effects on cognition in postmenopausal women, Hirshman et al. (2004) argue that the varied effects of sex steroids across tasks emphasize the significance of identifying the particular cognitive mechanisms influenced by sex steroids. However, studies of DHEA's impact on cortisol level and cognition tend to provide inconsistent results. A single dose of DHEA decreased cortisol but did not enhance verbal or visual memory in young males (Wolf, Köster, et al., 1997). Treatment with DHEA for 3 months decreased morning cortisol by 13.2% but did not change baseline cognition in 60 postmenopausal women (Barnhart et al., 1999). Surprisingly, administration of DHEA in a double-blind, placebo-controlled study was accompanied by an increase in free cortisol following a laboratory stress test and a decrease in visual memory (Wolf et al., 1998).

Thus, there are no methodologically sound studies to support the administration of DHEA to improve cognition that take into account the possible negative impact of cortisol on cognition. No studies have examined the complex relationship between cognition and 24-h DHEA(S) and cortisol levels. Further research in this area is needed before DHEA supplementation can be soundly recommended in older age groups.

The aim of this project was to follow up on the previous randomized, placebo-controlled double blind study by Kratz, which suggested that DHEA supplementation may have adverse cognitive effects in elderly women. Using

the same cognitive data, the authors analyzed additional 24-h measurements of DHEA, DHEAS, and cortisol in an attempt to elucidate the findings of Kratz. Specifically, they were interested in determining if the cognitive decrease with DHEA treatment found by Kratz is mediated by the impact of DHEA on endogenous cortisol.

The authors aimed to examine whether any relationship exists between serum 24-h DHEA(S) and cortisol levels and the cognitive abilities of post-menopausal women. It was hypothesized that: (1) cortisol is negatively associated with cognition at T1 and T2, (2) DHEAS is positively associated with cognition (as proposed by Kratz in his conclusions), and (3) the DHEA/cortisol ratio is positively associated with cognition. Data were utilized from a comprehensive neuropsychological test battery administered to study participants at baseline and study completion. Baseline hormone levels and cognitive functioning (T1) were compared to hormone levels and cognitive functioning at study completion (T2), following 6 months of daily DHEA supplementation.

METHODS

Participants

Twenty post-menopausal women (ages 46 to 66) participated in the study by Kratz after giving their written informed consent. Seventy percent were Hispanic, and 30 percent were primarily Caucasian. Eleven subjects were assigned to the treatment group (mean age = 52.1, SD = 4.3; mean education = 13.5 years, SD = 2.0). Nine subjects were randomly assigned to the placebo group (mean age = 52.3, SD = 5.9; mean education = 13.3 years, SD 2.2). The USC Institutional Review Board approved the test protocol and written consent form. Nineteen subjects were recruited through advertisement and word of mouth from the Los Angeles County Women's Hospital. One subject was recruited after mailing a letter that described the study to potential subjects identified from the USC Alzheimer's Disease Research Center (ADRC). All subjects were fluent in English.

Procedures

The study was performed in a randomized double-blind, placebo-controlled design. Eleven subjects received 25 mg DHEA supplements that they took

daily for 6 months, whereas the remaining 9 subjects took a placebo daily for 6 months. DHEA capsules were obtained from Hakala Apothecaries, Longwood, Colorado. Subjects were instructed to take one DHEA capsule or placebo capsule each morning at 8:00 AM.

Each subject came to the Los Angeles County Hospital for blood draws. The baseline and sixth month draws included about 1½ teaspoons of blood prior to taking the assigned capsule, and the same amount after 1, 2, 3, 4, 6, 8, 12, and 24 h. Blood draws required admittance to the research ward of the Los Angeles County Hospital, and were completed on the first and last day of the study for each participant. In addition to the blood draws, all subjects were expected to collect their urine the night before each of the blood draws.

Cognitive Testing

Baseline functioning was established on the morning of each subject's first visit. Subjects were re-tested in the afternoon (using alternate forms) of their 6 month visit. Neuropsychological tests included: California Verbal Learning Test (CVLT), Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Forward and Backward subtests, Trail Making Test A and B, Golden Stroop Test, Token Test, Category fluency, Boston Naming Test, Test of Nonverbal Intelligence-2 (TONI-2), and Judgment of Line Orientation.

Hormone Assays

Assays were conducted in the Reproductive Endocrine Research Laboratory at USC under the direction of Dr. Stanczyk. Each radioimmunoassay (RIA) method was validated extensively prior to use, with respect to assay sensitivity, accuracy, precision, and specificity. Each assay included three different levels of appropriate quality control samples: low, medium, and high.

Cortisol and DHEAS were quantified by direct RIA. DHEA was quantified by RIA following extraction and chromatography. A 0.2 ml aliquot of serum was combined with 1000 d.p.m. of ^{3}H-DHEA to follow procedural loss and was incubated for 30 min at 37ºC. DHEA was then extracted with diethyl ether and the subsequent extract was dried, reconstituted with isooctane and applied on a Celite partition column. Elution of DHEA was then performed, the elute was dried and the subsequent RIA utilizing ^{3}H-DHEA in conjunction with an anti-DHEA serum. Separation of antibody-bound and unbound DHEA was achieved by use of dextran-coated charcoal.

Statistical Analyses

in this randomized, placebo controlled, 6-month trial of DHEA replacement in post-menopausal women, it was previously established by Kratz that the treatment (DHEA) group showed a greater decrease in cognitive performance than the placebo group. The primary goal in this study was to determine if this cognitive decrease (group effect for DHEA) is mediated by the impact of DHEA replacement on endogenous cortisol. The authors examined variance within and between subjects in the treatment and placebo groups in 24-h cortisol levels, and then analyzed the associations between cortisol levels and cognitive measures. As no data on 24-h DHEA(S) levels are available for placebo subjects at this time, group effects for cortisol were solely examined. Additional consideration was given to 24-h DHEA(S) levels and cognitive performance for subjects in the treatment group. For all analyses, the level of significance for rejecting the null hypothesis of zero effect was set at $p = .05$. All analyses were performed using the program Statistica.

The relationship between cognitive performance and hormone fluctuation was determined by correlating MIN, MAX, and MAX-MIN hormone levels and cognitive test outcome variables at T1 and T2. The relationship between overall hormone level throughout the day and cognition was achieved by correlating average 24-h hormone levels with cognitive performance at T1 and T2.

RESULTS

Means and standard deviations for subjects' descriptive characteristics are displayed in Table 1. *T*-tests only revealed significant differences between groups in weight ($t[16] = –2.07$, $p = .05$). However, they do not significantly differ in body mass index ($t[16] = –1.36$, $p = .19$). Table 2 displays the MIN and MAX DHEA(S) levels. Correlations among MIN, MAX, MAX-MIN, and VAR hormone levels at T1 and T2 are provided in Table 3.

At T1, cortisol levels were higher in the treatment group at PM ($t[18] = –2.63$, $p = .02$). At T2, cortisol levels were higher in the treatment group at 11 AM ($t[18] = –2.19$, $p = .04$) and 12 PM ($t[18] = –2.93$, $p = .01$). Regardless of group, 8 AM cortisol levels changed over time for all subjects, as indicated by a significant occasion main effect [$F(1,17) = 6.52$; $p = .02$].

Treatment group DHEA levels were significantly greater at T1 than at T2 at most hours of measurement, including: 8 AM [$F(1,8) = 7.19$; $p = .03$], 9 AM [$F(1,7) = 5.31$; $p = .05$], 10 AM [$F(1,7) = 7.07$; $p = .03$], 11 AM [$F(1,9) =$

Table 1. Descriptive statistics for placebo and DHEA treatment (Tx) groups

	Placebo group		Tx group	
Descriptive variable	*M*	(*SD*)	*M*	(*SD*)
N	9		11	
Age	52.33	(5.94)	52.09	(4.30)
Education	13.33	(2.18)	13.45	(1.97)
Weight in kilograms	73.38	(12.15)	90.31	(21.25)*
Body mass index	30.57	(5.06)	34.46	(8.11)
Live births	2.67	(1.87)	2.40	(1.17)
# Past users of hormone replacement	0.56	(0.53)	0.40	(0.52)
# Current smokers	0.11	(0.33)	0.10	(0.32)
# Subjects reporting regular ETOH use	0.22	(0.44)	0.10	(0.32)

The body mass index is defined as weight (kilograms) divided by height (meters) squared. "Regular ETOH use" is defined as consumption of more than one alcoholic drink per week. *M* = mean, *SD* = standard deviation.

*$p < .05$.

Table 2. Mean circadian DHEA(S) parameters (MIN, MAX, MAX-MIN, and VAR) at T1 and T2 in the treatment group

	T1		T2		Change		
Variable	*M*	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	*p*
DHEA	1.73	(0.79)	2.40	(0.84)	0.80	(0.42)	.0002
MIN	4.45	(1.97)	5.00	(1.94)	0.90	(0.99)	.02
MAX	2.73	(1.42)	2.60	(1.35)	0.10	(0.99)	ns
MAX-MIN	0.94	(0.30)	0.81	(0.23)	–0.09	(0.31)	ns
VAR							
DHEAS							
MIN	1.18	(0.40)	1.80	(0.63)	0.60	(0.70)	.02
MAX	3.18	(0.75)	4.10	(1.10)	0.90	(0.99)	.02
MAX-MIN	2.00	(0.77)	2.30	(0.82)	0.30	(1.06)	ns
VAR	0.94	(0.25)	0.79	(0.18)	–0.16	(0.37)	ns

ns = not significant.

Table 3. Correlations among circadian parameters for treatment and placebo groups from T1 to T2

	Cortisol		DHEA		DHEAS	
Correlation variables	*r*	(*p*)	*r*	(*p*)	*r*	(*p*)
MIN at T1 +MIN at T2						
Treatment	.11	(ns)	.87	(.001)	.17	(ns)
Placebo	–.10	(ns)				
MAX at T1 +MAX at T2						
Treatment	.39	(ns)	.86	(.001)	.48	(ns)
Placebo	.14	(ns)				
MAX-MIN at T1 + MAX-MIN at T2						
Treatment	.26	(ns)	.71	(.02)	.17	(ns)
Placebo	.20	(ns)				
VAR at T1 + VAR at T2 –.27 (ns)	.50	(ns)	–.09	(ns)		
Treatment	.14	(ns)				
Placebo						

ns = not significant.

20.73; p =.00l], 12 PM [$F(1,9) = 20.73$; $p = .001$], 4 PM [1,9) = 5.36; $p = .05$], 8 PM [$F(1,9) = 6.11$; $p = .04$], and the average 24-h level [$F(1,6) = 7.83$; $p = .03$], suggesting a direct effect of treatment on endogenous DHEA. Treatment did not impact the ratio of DHEA/cortisol, as indicated by a nonsignificant difference in levels at T1 and T2 [$F(1,5) = 1.24$; $p = .32$].

Treatment group DHEAS levels were significantly greater at T2 than at T1 (baseline) at most hours of measurement: 8 AM [F(1,8) = 18.64; $p = .003$], 9 AM [$F(1,7) = 5.84$; $p = .05$], trend at 10 AM [$F(1,7) = 4.39$; $p = .07$], 11 AM [$F(1,9) = 17.57$; $p = .002$], 12 PM [$F(1,9) = 31.49$; $p = .0003$], 2 PM [$F(1,9) = 35.74$; $p = .0002$], 4 PM [$F(1,9) = 10.09$; $p = .01$], 8 PM [$F(1,9) = 6.92$; $p = .03$], and the average 24-h level [$F(1,6) = 9.90$; $p = .02$], again suggesting a direct effect of treatment on endogenous DHEAS.

Only one significant correlation was found among MIN, MAX, and MAX-MIN cortisol levels and cognitive measures for all subjects at T1: MIN cortisol was significantly negatively correlated with subjects' Digit Span Forward Raw score ($r = –.45$, $p = .05$). Correlations between average 24-h cortisol levels and cognitive performance at T1 revealed average cortisol to be significantly positively correlated with Trails B Errors ($r = .49$, $p = .05$), CVLT middle items ($r = .47$, $p = .05$) and negatively correlated with CVLT recency items ($r = –.45$, $p = .06$).

Nine significant correlations were found among MIN, MAX, and MAX-MIN cortisol levels and cognitive measures for subjects in the **treatment** group at T2. MIN cortisol levels were significantly positively eon-elated with treatment subjects' Digit Span Backwards raw scores (r = .68, p = .02), Digit Span Backwards span scores (r = .68, p = .02), and CVLT long delay free recall total scores, LD Free Total (r = .69, p = .02). MAX cortisol levels were significantly positively correlated with treatment subjects' performance on CVLT Trials 1–5 (r = .61, p = .04), CVLT Trial B (r = .60, p = .05), and CVLT long delay free recall items (r = .68, p = .02). MAX-MIN cortisol levels were significantly positively correlated with treatment subjects' performance on CVLT Trials 1–5 (r = .60, p = .05), CVLT long delay free recall, CVLT LDFR (r = .62, p = .04), and CVLT LD Free Total (r = .62, p = .04). In the **placebo** group at T2, three significant correlations were found among MIN, MAX, and MAX-MIN cortisol levels and cognitive measures. MIN cortisol was significantly negatively correlated with performance on the TONI (r = –.74, p = .02). MAX and MAX-MEN were both significantly positively correlated with CVLT LD Free total performance in the placebo group at T2 (r = .86, p = .003; r = .82, p = .007), respectively.

Correlations between average cortisol levels and cognitive measures at T2 for the treatment group, revealed average cortisol to be significantly positively correlated with Digit Backwards Span score (r = .72, p = .04), CVLT Intrusions during cued recall (r = .78, p = .02) and total CVLT Intrusions (r = .78, p = .02), CVLT BTOA (r = .88, p = .004), and CVLT Long Delay Free Recall Total (r = .72, p = .04). In the **placebo** group, average cortisol was significantly positively associated with CVLT Long Delay Free Recall Total (r = .71, p = .03) and significantly negatively associated with Digit Span Forward Raw scores (r = –.66, p = .05).

At T1, 4 significant correlations were found between DHEA levels and cognition. MIN DHEA was significantly negatively correlated with performance on the Token Test (r = –.66, p = .03), Stroop Word (r = –.65, p = .03), and Stroop Interference (r = –.60, p = .05) and significantly positively correlated with CVLT semantic recall (r = .64, p = .03).

Average DHEA was significantly negatively correlated with the Token Test (r = –.61, p = .05) and Digits Backwards Raw score (r = –.63, p = .04).

At T2, the number of significant correlations between DHEA and cognition increased to 7. MIN DHEA was significantly negatively correlated with performance on the BNT (r = –.79, p = .006), Stroop Color (r = –.67, p = .03), and JLO (r = –.74, p = .01) and significantly positively correlated with CVLT intrusions during free recall of items (r = .68, p = .03). MAX DHEA

was significantly positively correlated with Trails B Errors (r = .69, p = .03) and CVLT semantic items (r = 64, p = .05). MAX-MIN DHEA was also significantly positively correlated with CVLT semantic items (r = .72, p = .02).

Correlations between average DHEA and cognition at T2 revealed average DHEA to be significantly positively correlated with errors during Trails B performance (r = .80, p = .03) and use of semantic clustering on the CVLT (r = .78, p = .04). At T2, average DHEA was significantly negatively correlated with BNT (r = –.82, p = .02), Stroop Word (r = –.7 8, p = .04), and JLO (r = –.82, p = .02) performance. The DHEA/cortisol ratio was significantly negatively correlated with Digits Backwards Raw score (r = –.66, p = .05) and Span score (r = –.66, p = .05).

The DHEA/cortisol ratio at T2 was significantly negatively associated with Digit Backwards Raw (r = –.93, p = .003) and Span scores (r = –.91, p = .005), serial recall of CVLT items (r = –.82, p = .03), and CVLT Long Delay Free Recall total (r = –.8 1, p = .03). The DHEA/cortisol ratio tended to be positively associated with CVLT semantic clustering (r = .67, p = .10).

At T1, one significant correlation among MIN, MAX, and MAX-MEN DHEAS levels and cognitive performance was found: MIN DHEAS was significantly positively correlated with CVLT short delay Free total performance (r = .70, p = .02).

At T2, four significant correlations were found between DHEAS levels and cognition. MAX DHEAS was significantly negatively correlated with BNT performance (r = –.72, p = .02). MAX-MIN DHEAS was significantly positively correlated with Trials B errors (r = .68, p = .03) and significantly negatively associated with Stroop Color reading (r = –.70, p = .02) and Digit Span Forwards raw scores (r = –.73, p = .02). Average DHEAS was significantly negatively correlated with BNT performance at T2 (r = –.81, p = .03).

DISCUSSION

The present study investigated the impact of DHEA supplementation on total (combined free, albumin-bound, and CBG-bound) serum cortisol levels and cognition in postmenopausal women. Although DHEA does slightly increase cortisol levels at several time points and blunt cortisol's diurnal rhythmicity, results suggest that DHEA has a direct negative impact on cognition that is not mediated by its relationship to cortisol.

Cortisol was found to be positively associated with performance in two cognitive domains in the treatment group at T2, DHEAS was found to be

negatively correlated with cognition at T1 and T2, and the DHEA/cortisol ratio is negatively correlated with cognition at T1 and T2. The only apparent benefit from endogenous hormones at baseline is a positive association between both cortisol and DHEAS and short delay verbal recall, a benefit that seems far outweighed by the decreases in attention, mental tracking, language processing, and language output that are associated with cortisol and DHEA(S). At study completion, cortisol is the only hormone that is (unexpectedly) positively associated with cognitive functioning (in the domains of verbal memory and complex attention/mental tracking), whereas it is also associated with poor performance on tests of executive control, nonverbal intelligence, and visuospatial skills. With treatment, the negative associations between DHEA(S) and cognition only increase, including difficulties with attention, mental tracking, naming, nonverbal intelligence, and visuospatial tracking.

The effects of 25 mg oral DHEA on 24-h hormone levels and cognition in 20 postmenopausal women were assessed. Following treatment, an increase in cortisol was found at several time points, an alteration of cortisol's circadian rhythm, and an increase in the positive associations between cortisol and cognition. DHEA and its sulfate were negatively correlated with cognition at baseline, with an increasing number of negative associations at study completion. A rationale for these unexpected findings includes differences in the baseline hormone levels of the subjects compared to other groups of postmenopausal women, administration of a lower dose of DHEA, unknown impact of treatment on steroidogenesis, and a negative impact on neural functioning that is not explained by animal models.

Given the finding that DFIEA increases cortisol and flattens its diurnal pattern, DHEA is not recommended as an antidote to the harmful effects of GC administration. Exogenous cortisol is widely prescribed by the medical community for its anti-inflammatory effects in the treatment of allergic, autoimmune, rheumatologic, and neurologic diseases. However, excessive or long-lasting circulating levels of glucocorticoids tend to impact physical and psychological functioning, including higher order cognitive functioning negatively (Martignoni et al., 1992). Recently, the practice of glucocorticoid administration has been questioned, especially in the treatment of patients with neurologic disorders, because of a possible negative impact on cognitive functioning (Martignoni et al., 1992).

One solution to this dilemma has been suggested by Robinzon and Cutolo (1999). Because the deleterious side-effects of glucocorticoids emerge from both their direct catabolic activity and the suppression of DHEA production,

Robinzon and Cutolo proposed that DHEA replacement therapy may reduce damage caused by chronic glucocorticoid administration. Other researchers have also proposed the administration of low doses of DHEA in non-aged patients with low levels of endogenous DHEA, including with the administration of GCs (Casson et al., 1997, 1998). Although the authors cannot speak to the physiological effects of DHEA treatment, given the results of our study, DHEA replacement is not suggested as an antidote to the neuropsychological complications associated with administration of cortisol. Although DHEA may mitigate the negative effects of cortisol on cognition, its possible direct negative effects prevent it from being a useful antidote. Future research is needed to clarify the cognitive effects associated with the coadministration of DHEA and glucocorticoids.

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