0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 7
Printed in U.S.A.

COMMENTS

Effects of a Two-Week Physiological Dehydroepiandrosterone Substitution on Cognitive Performance and Well-Being in Healthy Elderly Women and Men*

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ABSTRACT

The levels of dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS decrease with age after a peak around 25 yr. Animal studies as well as the first studies in humans have generated the idea that DHEA replacement in elderly subjects may have beneficial effects on well-being and cognitive functions. In the present experiment 40 healthy elderly men and women (mean age, 69 yr) participated in a double blind, placebo-controlled DHEA substitution study. For 2 weeks subjects took 50 mg DHEA daily, followed by a 2-week wash-out period and a 2-week placebo period. The treatment sequence was randomized in a cross-over design. After 2 weeks of DHEA or placebo, psychological and physical well-being as well as cognitive performance were assessed using several questionnaires and neuropsychological tests. All subjects had low DHEAS baseline levels. DHEA substitution lead to a 5-fold increase in DHEAS levels in women (from 0.67 ± 0.1 to 4.1 ± 0.4 μg/mL; $P < 0.001$) and men (from 0.85 ± 0.1 to 4.5 ± 0.4 μg/mL; $P < 0.001$). DHEA, androstenedione, and testosterone levels also increased significantly in both sexes (all $P < 0.001$). No significant changes were observed in insulin-like growth factor I or insulin-like growth factor-binding protein-3 levels.

DHEA replacement had no strong beneficial effect on any of the measured psychological or cognitive parameters. Only women tended to report an increase in well-being ($P = 0.11$) and mood ($P = 0.10$), as assessed with questionnaires. They also showed better performance in one of six cognitive tests (picture memory) after DHEA. However, after Bonferroni α adjustment, this difference was no longer significant. No such trend was observed in men ($P > 0.20$). Likewise, no beneficial effects of DHEA substitution could be observed in any of the other tests of the neuropsychological test battery in either sex (all $P > 0.20$). In conclusion, the present data do not support the idea of strong beneficial effects of a physiological DHEA substitution on well-being or cognitive performance in healthy elderly individuals. (*J Clin Endocrinol Metab* **82:** 2363–2367, 1997)

THE ADRENAL hormone dehydroepiandrosterone (DHEA), with its sulfate conjugate DHEAS, is the most abundant steroid hormone in man. It is produced not only in the adrenals and testis, but also seems to be metabolized in the central nervous system (CNS) (1). The DHEA concentration in blood steadily declines with advancing age after a maximum between 20–30 yr (2). Animal studies have demonstrated improved memory after DHEA and DHEAS administration in young (3, 4) and old (5) mice. In addition, DHEAS enhances hippocampal plasticity (6). One possible explanation for the memory-improving effects of DHEAS in rodents is that it exerts effects on the CNS by acting as an antagonist on the γ-aminobutyric acid-A receptor (7) and as an agonist on the σ receptor (8).

Replacement studies investigating endocrine or immunological changes in enhanced DHEA levels have been conducted in elderly humans (9–11). In none of these experiments were data on psychological changes during DHEA administration reported. In a recent experiment Morales *et al.* (12) observed that after 3 months of DHEA replacement (50 mg/day), 67% of men and 84% of women reported an increase in psychological well-being, as observed in unstructured interviews. A similarly beneficial effect of DHEA substitution on well-being in morbidly obese adolescents could not be found in a more recent study by Vogiatzi *et al.* (13).

Epidemiological studies trying to link DHEAS levels and cognitive performance in elderly humans reported divergent results (14, 15). An open labeled clinical trial in six elderly patients with major depression reported memory and mood improvement after DHEA treatment (16). A first placebo-controlled experiment in young healthy men did not find positive effects of DHEA on memory performance (17).

Received January 8, 1997. Revision received March 14, 1997. Accepted March 20, 1997.

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* This work was supported by a research grant from the Deutsche Forschungsgemeinschaft (He 1013/13–1).

As DHEA and DHEAS concentrations decline with age, and DHEA seems to exert such a broad variety of beneficial effects in rodents, the idea of DHEA as a possible "fountain of youth" is now being discussed [see editorial by Baulieu (18)]. However, as only the adrenal cortex of primates produces larger amounts of DHEA (19, 20), extrapolation from results obtained in subprimate species to humans is difficult. The present study thus was performed to investigate possible effects of a physiological DHEA replacement on cognitive performance and well-being in healthy elderly women and men.

Subjects and Methods

Forty-six elderly subjects participated in the present experiment, with 40 subjects completing the 6-week study period. Six subjects dropped out due to illness (flu or rheumatoid arthritis) or noncompliance with treatment. The remaining 25 men (mean age ± SE, 69.4 ± 1.2 yr) and 15 women (69.1 ± 1.7 yr) were all nonobese (body mass index, 26.0 ± 0.6 for men; 25.2 ± 0.9 for women). About 30% of the subjects (5 women and 9 men) were medication free; the others took medication typically found in an elderly population (*e.g.* cardiac drugs and hypotensives) (21). Four of the 10 women taking medication received treatment with estrogens for postmenopausal complaints. Subjects were recruited via the local newspaper and were paid for participation. All subjects gave written informed consent to participate in the present experiment. The study protocol was approved by the University of Trier ethics committee.

The study was performed in a double blind, placebo-controlled design. The two treatment periods of 2 weeks each (placebo or 50 mg/day DHEA) were separated by a 2-week washout period. Half of the subjects received placebo first, and the other half received DHEA. Subjects were instructed to ingest one DHEA or placebo capsule each night at bedtime. One DHEA capsule (Prasteron, Audor Pharma, Regensburg, Germany) contained 50 mg DHEA and lactose; placebo capsules contained lactose only.

Every subject had four appointments at the laboratory, one before and one after each treatment period. At each of the four appointments a blood sample was obtained for hormone analysis. After each of the two treatment periods, subjects had to complete questionnaires as well as a neuropsychological test battery developed for testing elderly subjects (see below). On the two test sessions parallel versions of the tests were used. Testing was performed between 0800–1200 h. Each subject was tested at the same time of day by the same investigator.

Assessment of well-being and mood

A quality of life questionnaire (22) for assessment of psychological and physical complaints in individuals of advanced age was used. In this test higher test scores indicate lower quality of life (test score range, 39–116).

A mood questionnaire (23) was used to assess elevated *vs.* depressed mood, wakefulness *vs.* sleepiness, and calmness *vs.* restlessness.

The German short version of the Center for Epidemiological Studies Depression Scale (24) was employed to measure depression.

In an unstructured interview, subjects were asked to report any changes in their physical or psychological conditions during the past 2-week period. If changes were reported, subjects rated the intensity of these changes.

Neuropsychological tests

A broad variety of tests was used to assess different aspects of cognitive performance (speed as well as power aspects, short and long term memory). Tests 2–5 are part of a standardized test battery for the assessment of cognitive performance in elderly subjects (22). The test material is especially designed for this population (*e.g.* text printed in larger fonts).

Concentration. In the age concentration test (25), the subject has to cross out a specified target item (a half-circle) of several similar looking distractor items (half-circles that differ in color and/or position). The time for completion as well as the amount of correct decisions are measured.

Visual short and long term memory (picture memory test). Fourteen pictures showing everyday objects (*e.g.* fruits or clothes) were presented at a rate of one picture every 2 s. Immediate and delayed (15 min later, after test 5) free recalls were assessed.

Stroop test (26). The classical version with three cards was used. For each card the time needed to read the items (*e.g.* name the colors on cards 2 and 3) was recorded, and the difference between cards 3 and 2 was used as the test score.

Digit span (number rehearsal forward and backwards). Series of digits were read to the subjects, which they had to repeat. If a subjects failed on two consecutive trials the test was stopped, and the highest number of digits correctly repeated was used as the test score.

Psychomotoric speed (number connecting). Here the subject has to connect with a pencil numbers on a piece of paper (from 1–30) as fast as possible. Two test sheets were used in each session, and the mean time needed for completion of the task was used as the test score.

Auditory verbal learning test (27, 28). A list of 15 words was read to the subjects 4 times. Immediate recall was tested after each presentation. Thereafter, a second list was presented only once, with immediate recall being tested; delayed recall of the first list was then tested. This test is an indicator of verbal memory; the total number of words recalled as well as the slope of the learning curve and the amount of interference produced by the second list can be evaluated.

Hormone assays

At all four appointments blood was collected from the subjects for hormone analyses. Plasma DHEAS levels were measured at all four appointments, DHEA, androstenedione (A'dione), testosterone (T), insulin-like growth factor I (IGF-I), and IGF-binding protein-3 (IGFBP-3) levels were assessed only after each treatment period. The following commercially available assays were used: DHEAS (enzyme-linked immunosorbent assay; IBL, Hamburg, Germany), DHEA and A'dione (RIA; IBL), T (Delfia, Pharmacia, Freiburg, Germany), and IGF-I (RIA; BioMerieux, Marcy-l'Etoile, France). IGFBP-3 levels were determined using an in-house time-resolved immunoassay with fluorescence detection, as described previously (29). The sensitivity of the assays were 0.05 μg/mL for DHEAS, 0.009 ng/mL for DHEA, 0.02 ng/mL for A'dione, 0.1 ng/mL for T, 0.02 ng/mL for IGF-I, and 10.9 μg/L for IGFBP-3, respectively. The inter- and intraassay coefficients of variations were 7% and 8% for DHEAS, 4% and 8% for DHEA, 5% and 7% for A'dione, 8% and 9% for T, 3.8% and 5.7% for IGF-I, and 3.5% and 11.7% for IGFBP-3, respectively. Of additional note is that the cross-reactivity of the DHEA RIA for DHEAS is less than 0.02%.

Statistical analyses

Hormone data were analyzed by ANOVA, with the two factors sex (two levels) and treatment (two levels). *Post-hoc* comparisons were performed using Newman-Keuls tests. Cognitive as well as psychological data were analyzed by two-tailed Student's *t* test for correlated samples for each sex separately.

Results

Steroid hormones

The effects of DHEA replacement on steroid hormones are summarized in Table 1. ANOVA showed that DHEAS, DHEA, A'dione, and T levels increased significantly ($P < 0.001$) in response to DHEA treatment in both sex. DHEAS levels did not differ for baseline, washout, and placebo treatment periods (see Table 1 for F values of the treatment main effect).

TABLE 1. Hormone levels in women and mean after 2 weeks of placebo or DHEA administration

	Women			Men			Treatment effect
	Placebo	DHEA	% Increase	Placebo	DHEA	% Increase	F(1,38)
DHEAS (μg/mL)	0.67 ± 0.1	4.1 ± 0.4[a]	511	0.85 ± 0.1	4.5 ± 0.4[a]	429	141.3
DHEA (ng/mL)	3.5 ± 0.4	8.1 ± 0.5[a,b]	131	2.85 ± 0.2	5.86 ± 0.3[a]	105	250.4
A'dione (ng/mL)	0.85 ± 0.1	1.55 ± 0.1[a]	82	1.06 ± 0.1[c]	1.55 ± 0.1[a]	46	99.9
T (ng/mL)	0.19 ± 0.1	1.2 ± 0.1[a]	531	4.75 ± 0.4[c]	6.0 ± 0.5[a,c]	26	33.1
IGF-1 (ng/mL)	96.3 ± 9.3	104.1 ± 6.5	8	120.3 ± 6.9	122.3 ± 8.2	1.7	1.56
IGFBP-3 (μg/L)	3.4 ± 0.2	3.4 ± 0.2	0	3.4 ± 0.2	3.5 ± 0.2	2.9	0.00

[a] Significant increase compared to placebo ($P < 0.001$).
[b] Women significantly higher than men ($P < 0.01$).
[c] Men significantly higher than women ($P < 0.01$).

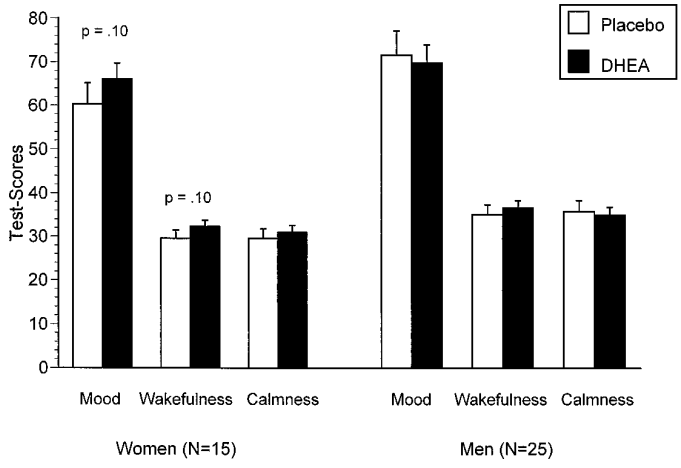

FIG. 1. Effects of DHEA substitution on mood (test score range, 0–80 for mood; 0–40 for wakefulness and calmness).

IGF-I and IGFBP-3

The results are summarized in Table 1. IGF-I levels did not change in men or women after DHEA treatment, although a small, but nonsignificant, trend toward an increase was observed ($F = 1.56$; $P > 0.20$). IGFBP-3 levels were unaltered in men and women.

Mood and well-being

No significant changes in any of the questionnaires used to assess mood or well-being was observed for the total group. However, a trend toward an increase in quality of life was found in women, as indicated by a decrease in the number of psychological and physical complaints (74.5 ± 6 after placebo *vs.* 67.2 ± 4 after DHEA; $t = 1.68$; $P = 0.11$). In addition, a trend toward increased mood and wakefulness was observed in this group ($t = 1.7$; $P = 0.10$ for both comparisons; Fig. 1). No such changes were seen in men. No changes were observed in the depression scale (both $t < 1$); however, most of the subjects already had very low depression scores at baseline.

Eight men (32%) and eight women (53%) reported changes in physical or psychological conditions during DHEA substitution in the open interviews. These changes were usually rated as mild (except for four cases: one woman and three men) and included positive as well as negative observations, *e.g.* increased well-being, increased activity, increase in libido or sexual potency, changes in sleep quality (increase as well as decrease), hot flashes, and chest pain. Three men (12%) and nine women (60%) reported changes during placebo, with increased fatigue being most frequently mentioned. Women reported more changes under both conditions. Whereas under DHEA more positive changes were reported, more negative changes where perceived under placebo (see Table 2 for details).

Cognitive tests

The results of the neuropsychological test battery are shown in Table 3. There was no overall increase in performance after DHEA substitution. In none of the six tests were significant changes observed in men. In women, an increase in performance in the picture memory test was found under both recall conditions (immediate recall: $t_{14} = -2.7$; $P < 0.05$; delayed recall: $t_{14} = -2.38$; $P < 0.05$). It should be noted, however, that after Bonferroni α correction for multiple comparisons, the adjusted α level is $P = 0.0056$, given that nine comparisons were made for each sex. Thus, the observed difference in picture memory after DHEA treatment can no longer be considered statistically significant. In addition to the total number of recalled words, the auditory verbal learning test was analyzed using an ANOVA, with the three factors sex, treatment, and level of practice. However, neither treatment main effect nor treatment by level of practice interaction was significant (all $F < 1$).

Discussion

This is the first study to investigate the effects of a physiological DHEA substitution on well-being, mood, and cognitive performance in elderly subjects using standardized questionnaires and well evaluated test materials. We were unable to observe an overall significant beneficial effect on self-report measures or cognitive abilities in our sample of 40 healthy adults of advanced age. Only in women was there a trend toward increased quality of life and a better performance in one (picture memory task) of six cognitive tasks after DHEA treatment. However, these positive results should be viewed with great caution because the number of tests employed calls for α correction to avoid type I errors. In the unstructured interview, 32% of the men and 53% of the women reported changes during DHEA substitution. The reported changes after DHEA differed markedly for each individual, with both positive as well as negative changes reported. Only 4 of 40 participants (1 woman and 3 men) perceived a marked improvement in well-being and physical activity.

TABLE 2. Self-reported changes in the subjects after 2 weeks of placebo or DHEA

Case no.	Sex	Age (yr)	BMI	Reports after placebo	Reports after DHEA
1	m	61	28.4		
2	m	62	25.3		
3	m	77	29.3		Return to spontaneous penile erection
4	m	73	20.2		
5	m	73	28.0		
6	m	65	23.8		Increased fatigue
7	m	73	22.7		
8	m	68	28.3		Slightly increased well-being
9	m	67	23.0		
10	m	74	27.0	Mood problems	Increased sleep quality, more active[a]
11	m	72	24.5		
12	m	64	27.4		
13	m	66	24.4		Increased activity, sleep quality, sleep time, and sex desire[a]
14	m	68	24.8		Increased sexual potency
15	m	74	28.4	Headaches	
16	m	72	24.5		
17	m	58	24.8		
18	m	67	35.3		Increased sleep quality
19	m	72	26.1		More active, more euphoric[a]
20	f	71	27.3	Stomach problems	Chest pain, increased sexual desire
21	f	60	28.7	More tired, depressed mood	Disrupted sleep
22	f	72	23.8	More tired	Less tired, reduced sleep time
23	f	70	27.6		
24	f	69	22.3		Hot flashes, weight gain, poorer digestion
25	f	73	24.6		More awake, leg cramps at night
26	m	66	24.1		
27	f	72	25.7	Increased hunger, weight gain	Increased well-being and concentration, "nicer" dreams
28	f	58	28.7	Joint pain, poorer mood	Increased activity, poorer sleep[a]
29	f	71	25.0	More tired	More tired
30	m	81	23.4		
31	m	67	24.5		
32	m	83	23.4	More active and euphoric	
33	f	74	20.4		
34	f	64	24.4	Allergic skin reaction	Headaches, allergic skin reaction
35	m	67	27.9		Poorer sleep, increased nightly urination, hot flashes
36	f	65	31.6	Poorer sleep	
37	f	82	20.7		
38	f	60	26.5	Heartburn	
39	m	66	29.7		
40	f	76	20.0		

[a] Marked self-perceived changes.

TABLE 3. Neuropsychological tests results

Tests	Men (n = 25)			Women (n = 15)		
	Placebo	DHEA	*P* level	Placebo	DHEA	*P* level
Age concentration test						
Time (s)	69.1 ± 2.4	68.8 ± 2.7	NS	70.0 ± 4.9	72.1 ± 4.5	NS
Correct decisions (max. 40)	38.8 ± 0.2	37.8 ± 0.8	NS	39.1 ± 0.3	38.1 ± 0.7	NS
Picture memory						
Immediate recall	8.5 ± 0.3	8.8 ± 0.4	NS	8.7 ± 0.4	9.5 ± 0.4	0.01[a]
Delayed recall	6.8 ± 0.4	7.1 ± 0.4	NS	7.2 ± 0.3	8.1 ± 0.5	0.03[a]
Stroop						
Interference (s) (difference in Table 3 minus Table 2)	19.8 ± 1.5	21.6 ± 1.7	NS	17.7 ± 2.2	18.2 ± 1.8	NS
Digit span						
Forward	6.8 ± 0.2	6.5 ± 0.3	NS	6.7 ± 0.3	6.3 ± 0.3	NS
Backwards	4.6 ± 0.2	4.7 ± 0.3	NS	4.7 ± 0.3	5.1 ± 0.3	NS
No. connection						
Time (s)	25.9 ± 1.4	25.7 ± 1.5	NS	21.4 ± 0.9	22.1 ± 1.5	NS
Auditory verbal learning test						
Total amount of words recalled	50.8 ± 2.0	52.0 ± 2.1	NS	54.0 ± 2.3	54.4 ± 1.9	NS

NS, $P > 0.20$.
[a] Not significant after Bonferoni alpha adjustment.

The present findings support recent findings by Vogiatzi *et al.* (13), who failed to observe significant effects of DHEA on well-being in morbidly obese adolescents. On the other hand, our results contradict previous findings in elderly subjects (12). With similar effects on sex steroid levels as described in this study, Morales *et al.* (12) reported a marked

increase in well-being in 84% of the women and 67% of the men after 3 months of 50 mg/day DHEA treatment, suggesting a large effect of DHEA substitution on well-being. Of course, the experimental protocols of the two studies differ to some degree. First, in the present study subjects were substituted for 2 weeks instead of 3 months using the same dose. The rational for the chosen strategy was that if DHEA(S) would indeed exert its effects on well-being or cognition as a neurosteroid, as suggested by others (1, 7), this should lead to significant treatment effects within only a few days. Direct effects of DHEA(S) on the γ-aminobutyric acid-A receptor in the CNS (7) or a genomic effects of the biologically active androgen metabolites A'dione or T should have been detectable after 2 weeks of DHEA administration (30). Animal studies indeed found memory-enhancing effects of DHEA after even a single application (3–5). A second difference between the two studies was the use of standardized questionnaires and test material to investigate changes in psychological parameters in the present study. Despite the use of elaborated psychological test material, no overall beneficial effect of DHEA treatment could be observed in the present study. In addition, with more subjects investigated here (and the same double-blind cross-over study design), the probability of detecting changes in psychological parameters was very high given the effect size of DHEA substitution reported by Morales and co-workers (12).

With respect to the IGF system, a 2-week DHEA treatment does not seem sufficient to enhance IGF-I. A prolonged treatment period of 3 months, however, significantly increased the level of bioavailable IGF-I by a simultaneous rise in IGF-I and a decrease in IGFBP-1 (12). After 2 weeks of DHEA substitution, IGF-I levels tended to be higher than the respective baseline values without reaching statistical significance. It appears that DHEA achieves its effect on IGF-I through rather indirect mechanisms, which may take more than 2 weeks to develop. A rise in IGF-I could be necessary to produce beneficial effects of DHEA on well-being. GH or IGF-I administration to GH-deficient individuals has multiple beneficial effects (31), some of which are similar to the reported DHEA effects, including elevated mood, improved quality of life, and behavioral changes (32, 33). However, to date no studies have addressed this possible mechanism of DHEA action on psychological parameters.

The results of the present study do not support the idea of a strong direct effect of DHEA on cognition or well-being in healthy elderly subjects. Possible beneficial effects of DHEA might be indirect and are probably not the consequences of a direct action of DHEA on the CNS. Whether prolonged DHEA substitution in healthy elderly individuals affects psychological parameters remains to be shown.

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