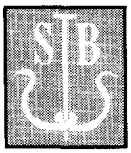

BRIEF REPORTS

A Single Administration of Dehydroepiandrosterone Does Not Enhance Memory Performance in Young Healthy Adults, but Immediately Reduces Cortisol Levels

Oliver T. Wolf, Birthe Köster, Clemens Kirschbaum, Reinhard Pietrowsky, Werner Kern, Dirk H. Hellhammer, Jan Born, and Horst L. Fehm

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Introduction

Dehydroepiandrosterone (DHEA), with its sulfate conjugate (DHEAS), is the most abundant steroid hormone in man (Orentreich et al 1984). It is released from the adrenals, but also seems to be directly synthesized in the central nervous system (Robel and Baulieu 1994), where it acts as a gamma-aminobutyric acid $(GABA)_A$ receptor antagonist (Majewska 1992) in animals. DHEA and DHEAS have been shown to increase neuronal excitability by reducing GABA-induced neuronal inhibition. These steroids therefore have been termed "excitatory neurosteroids" (Robel and Baulieu 1994; Majewska 1992). Results from animal studies further indicate that $GABA_A$-antagonistic drugs can improve memory (e.g., Castellano and McGaugh 1990). Indeed antiamnestic as well as memory-improving effects of DHEA and DHEAS could be demonstrated in mice (Flood et al 1988; Melchior and Ritzmann 1996). In the latter study, DHEA blocked the memory-impairing effects of ethanol. In addition, DHEAS enhanced hippocampal primed burst potentiation, which is an electrophysiological model of neuronal plasticity (Diamond et al 1996). In humans, a single administration of DHEA to young adults was found to increase REM sleep (Friess et al 1995). A first open-labeled clinical trial in 6 depressed elderly patients with low DHEA levels reported an improved memory and mood after subchronic DHEA treatment (Wolkowitz et al 1995); however, placebo-controlled studies in healthy subjects on the influence of DHEA on memory performance are still missing. Here we examined the effects of a single DHEA administration on memory performance in healthy men.

Methods and Materials

Thirty-six male university students (mean age 25.1 ± 0.5 years) participated in the experiment. All subjects were free of medication and nonobese (body mass index: 22.6 ± 0.3). The study was approved by the local ethics committee, and all subjects gave written informed consent. Each subject was tested on two consecutive days with parallel versions of the memory tests being used. On the first day, serving as individual baseline, all subjects received placebo. On the second day, half of the subjects (randomly assigned) received DHEA (300 mg dissolved in 5 mL of ethanol mixed with 100 mL juice), and the other half again received placebo (the same ethanol–juice mix) double-blind. Since DHEA is lipophilic, it was diluted in ethanol. Substances

From the Center for Psychobiological and Psychosomatic Research, University of Trier, Trier, Germany (OTW, CK, DHH); and Department of Neuroendocrinology, Medical University of Luebeck, Luebeck, Germany (BK, RP, WK, JB, HLF).

Address reprint requests to Clemens Kirschbaum, PhD, Center for Psychobiological and Psychosomatic Research, University of Trier, Dietrichstr. 10-11, 54290 Trier, Germany.

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Table 1. DHEA and DHEAS Concentrations following Administration of DHEA or Placebo

Time	DHEA (mg/L)		DHEAS (mg/dL)	
	Placebo (n = 18) (mean ± SEM)	DHEA (n = 18) (mean ± SEM)	Placebo (n = 18) (mean ± SEM)	DHEA (n = 18) (mean ± SEM)
−30 min	4.59 ± 0.45	5.69 ± 0.85	277.3 ± 35.7	314.2 ± 22.5
15 min	5.44 ± 1.10	27.69 ± 2.10[a]	278.0 ± 40.4	444.1 ± 36.5[a]
60 min	4.13 ± 0.43	15.42 ± 0.88[a]	250.0 ± 30.9	513.1 ± 36.0[a]
110 min	3.68 ± 0.22	9.43 ± 0.91[a]	249.4 ± 22.0	511.8 ± 27.3[a]

Repeated-measures ANCOVA, treatment main effect: DHEA: $F_{(1,33)} = 132.0$, $p < .001$; DHEAS: $F_{(1,33)} = 87.8$, $p < .001$.
[a]Newman–Keuls post hoc test, $p < .001$ for difference from placebo.

were administered 1 hour prior to memory testing, which took place between 11 PM and 12 AM, when endogenous plasma concentrations of DHEA are at their circadian nadir (Sjöberg et al 1979). Another advantage of the selected time was that memory performance is typically poorer in the late evening (Folkard et al 1985), so memory improvement by DHEA should not be blunted due to a possible ceiling effect in young adults. Blood samples were obtained 30 min before drug intake and 15, 60 (before memory testing), and 110 min (after memory testing) thereafter.

Memory Tests

DHEA improves memory in mice in several test paradigms (Flood et al 1988; Melchior and Ritzmann 1996). Since no studies in humans have been conducted so far, tests covering different types of memory (visual, verbal, and spatial declarative tasks) have been employed. For other steroid hormones differential effects on some memory forms are documented. Estrogen seems to modulate verbal memory, whereas testosterone influences spatial abilities (see for review: Kimura and Hampson 1994); another example is that cortisol selectively impairs declarative memory, while having no effects on procedural memory (Kirschbaum et al 1996).

The Auditory Verbal Learning Test (AVLT; Crawford et al 1989; Lezak 1983). A list of 18 tape-recorded words was repeatedly presented five times. Immediate recall of words was tested after each presentation. Thereafter, a different list was presented, which again had to be recalled immediately. Then delayed recall of the first list was tested.

Visual recognition. Forty-eight slides (16 food-related pictures, 16 sexually related pictures, 16 landscape pictures) were presented at a rate of one slide per second. Immediately after presentation a second series of 48 slides was presented, half of which were identical with the stimuli of the first series. These had to be recognized by the subject. False-positive and false-negative responses were summed to a single error score.

Spatial memory (Bäumler 1974). Subjects were asked to memorize (within 1 min) a route marked in a city map. Following performance on the Sternberg task (see below), the subject had to draw the learned route onto an unmarked map. The number of correctly chosen roads was determined and used as the test score. This task was one part of a standardized German test battery to evaluate different memory types.

Sternberg task (Sternberg 1966, 1975). Following a 30-sec presentation of memory sets consisting of one, two, or four letters, single letters were presented consecutively on a computer screen. The subject had to decide as fast and as accurately as possible whether this letter belonged to the memory set. Reaction time was measured for the three set sizes as well as for the two demanded reaction types. Reaction time in this task reflects speed of screening processes in short-term memory.

To evaluate whether possible changes in cognitive performance would be accompanied by changes in perceived mood and fatigue, an extensive adjective checklist was presented to the subjects immediately before memory testing (EWL; Janke and Debus 1978). The adjectives describe the subject's mood state on 15 different dimensions.

Serum DHEA, DHEAS, and cortisol concentrations were determined with commercial assay kits to validate treatment effects.

Effects of DHEA on memory performance and mood were evaluated by analysis of covariance (ANCOVA), including the test scores from the first session as covariates. This kind of analysis allows control for baseline differences between the treatment groups. Effects of DHEA treatment on blood hormone levels were also evaluated by a two-way ANCOVA with the grouping factor "treatment" and the repeated factor "time." Baseline hormone levels (−30 min) on the second day served as covariates. Post hoc analyses were performed for all significant effects by Newman–Keuls tests.

Results

Compared with placebo, DHEA administration significantly increased plasma concentrations of DHEA and DHEAS (Table 1).

Plasma cortisol concentrations were reduced by DHEA, as indicated by a significant treatment main effect [$F(1,33) = 4,8$; $p < .05$]. Post hoc tests revealed that the significant difference was observed 15 min after DHEA intake (mean ± SEM: 3.99 ± 0.8 mg/dL versus 5.87 ± 1.1 mg/dL for placebo).

Performance on all cognitive tests was comparable following intake of DHEA and placebo. The only difference showing a statistical trend ($p < .10$) was a slightly impaired visual recognition following DHEA. None of the tests indicated possible memory-enhancing effects of the steroid (Table 2).

DHEA also did not affect self-reported mood and fatigue (all

Table 2. Memory Performance in Subjects Treated with DHEA or Placebo

Test	Placebo group (n = 18) (mean ± SEM)	DHEA group (n = 18) (mean ± SEM)	F value	p level
Verbal learning				
Recalled words (averaged across all trials)	12.8 ± 0.5	12.4 ± 0.6		
Treatment main effect (df = 1,34)			0.55	.46
Treatment by trial interaction (df = 6,198)			0.64	.70
Visual recognition				
Errors (averaged across stimulus categories)	1.7 ± 0.3	2.3 ± 0.3		
Treatment main effect (df = 1,34)			3.27	.07
Treatment by category interaction (df = 2,68)			1.31	.28
Spatial memory				
Score of correct decisions (maximum: 31)	18.1 ± 1.6	17.6 ± 1.6	0.08	.77
Sternberg task				
Mean reaction time in milliseconds	511 ± 12.6	514 ± 15.0		
Treatment main effect (df = 1,34)			0.07	.79
Treatment by set size interaction (df = 2,66)			0.13	.87
Treatment by reaction type interaction (df = 1,33)			1.7	.20

Analysis of covariance: values from the first test session (all subjects placebo) served as covariates; presented means are baseline adjusted.

F values < 1). Only in the Sternberg test was a practice effect from day 1 to day 2 observed [$F(1,34) = 23.6$, $p < .001$], whereas no practice effect was obvious for the other three tests (all $p > .05$).

Discussion

Animal studies (Flood et al 1988; Melchior and Ritzmann 1996) as well as a first trial with patients (Wolkowitz et al 1995) have stimulated the hypothesis that DHEA improves memory functions. The present experiment in young healthy men does not support this notion. A single administration of DHEA had no effects on performance in several tests covering different aspects of memory. Increased plasma concentrations of DHEA and DHEAS after DHEA application as well as a transient decrease in cortisol levels assured that the exogenous DHEA was absorbed into the blood and was endocrinologically active. The decrease in cortisol levels following administration of DHEA supports the hypothesis of an "antiglucocorticoid" action of this steroid (see Kalimi et al 1994 for review).

The failure of DHEA to enhance memory performance raises serious doubts about an acute effect of this steroid on memory functions in young adults. Also indirect effects mediated via mood appear to be unlikely, since in the present study DHEA did not change self-reported mood and fatigue; however, it cannot be excluded that a different dose of DHEA and/or different memory tests might have yielded different results. Although subjects were tested around midnight, which is a diurnal time of lower cognitive performance, it cannot be excluded that potential improving effects of DHEA were masked in our sample of healthy young subjects due to ceiling effects; i.e., these subjects may have already performed close to their peak performance, not allowing any further improvement; however, at least in rodents DHEA enhances memory performance in young cognitively unimpaired animals (Flood et al 1988; Melchior and Ritzmann 1996). It remains also open whether the present observations after a single administration of DHEA in healthy young adults also apply to effects of longer-term replacement in DHEA-deficient individuals (e.g., elderly subjects, Morales et al 1994; or clinical patients, Wolkowitz et al 1995); however, we have just completed a 2-week DHEA replacement study in healthy elderly subjects and again did not find any evidence for improvement of cognitive performance by DHEA (Wolf et al 1997). Taken together, the present results suggest that DHEA has no immediate effect on memory functions in younger adults.

References

Bäumler G (1974): *Lern- und Gedächtnistest (LGT-3) Handanweisung.* Göttingen: Hogrefe.

Castellano C, McGaugh JL (1990): Effects of post-training bicuculline and muscimol on retention: Lack of state dependency. *Behav Neural Biol* 54:156–164.

Crawford JR, Stewart LE, Moore JW (1989): Demonstration of savings on the AVLT and development of a parallel form. *J Clin Exp Neuropsychol* 11:975–981.

Diamond DM, Branch BJ, Fleschner M (1996): The neurosteroid dehydroepiandrosterone sulfate (DHEAS) enhances hippocampal primed burst, but not long-term, potentiation. *Neurosci Lett* 202:204–208.

Flood JE, Smith GE, Roberts E (1988): Dehydroepiandrosterone and its sulfate enhance memory retention in mice. *Brain Res* 447:269–278.

Folkard S, Marks M, Minors DS, Waterhouse JM (1985): Circadian rhythms in human performance and affective state. *Acta Psychiatr Belg* 85:568–581.

Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F (1995): DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range. *Am J Physiol* 268:E107–E113.

Janke W, Debus G (1978): *Die Eigenschaftswörterliste EWL. Eine mehrdimensionale Methode zur Beschreibung von Aspekten des Befindens.* Göttingen: Hogrefe.

Kalimi S, Shafagoj Y, Lorai R, Padgett D, Regelson W (1994): Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). *Mol Cell Biochem* 131:99–104.

Kimura D, Hampson E (1994): Cognitive pattern in men and women is influenced by fluctuations in sex hormones. *Curr Dir Psychol Sci* 3:57–61.

Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH (1996): Stress- and treatment-induced elevation of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci* 58:1475–1483.

Lezak MD (1983): *Neuropsychological Assessment,* 2nd ed. New York: Oxford University Press.

Majewska MD (1992): Neurosteroids: Endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. *Prog Neurobiol* 38:379–395.

Melchior CL, Ritzmann RF (1996): Neurosteroids block the memory-impairing effects of ethanol in mice. *Pharmacol Biochem Behav* 53:51–56.

Morales AJ, Nolan JJ, Nelson JC, Yen SSC (1994): Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 78:1360–1367.

Orentreich N, Brind JL, Rizer RL, Vogelman JH (1984): Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 59:551–555.

Robel P, Baulieu E-E (1994): Neurosteroids biosynthesis and function. *Trends Endocrinol Metab* 5:1–8.

Sjöberg B, de la Torre B, Hedman M, Falkay G, Diczfalusy (1979): Circadian variation in systemic hormone levels in healthy men. *J Endocrinol Invest* 2:131–137.

Sternberg S (1966): High-speed scanning in human memory. *Science* 153:652–654.

Sternberg S (1975): Memory scanning: New findings and current controversies. *Q J Exp Psychol* 27:1–32.

Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, Dressendörfer RA, et al (1997): Effects of a two week physiological dehydroepiandrosterone (DHEA) substitution on cognitive performance and well being in healthy elderly women and men. *J Clin Endocrinol Metab* 82:2363–2367.

Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Ormiston S, et al (1995): Antidepressant and cognition-enhancing effects of DHEA in major depression. *Ann NY Acad Sci* 774:337–340.