

Effects of Dehydroepiandrosterone Replacement in Elderly Men on Event-Related Potentials, Memory, and Well-Being

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Background. In humans, concentrations of the adrenal steroid hormone dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decline with age. Results from studies in rodents have suggested that DHEA administration can improve memory performance as well as neuronal plasticity. However, a first study from our laboratory could not demonstrate beneficial effects of DHEA substitution on cognitive performance and well-being in elderly subjects. To further evaluate whether DHEA replacement has effects on the central nervous system, an experiment using event-related potentials (ERPs) was conducted.

Methods. In this placebo-controlled crossover study, 17 elderly men (mean age, 71.1 ± 1.7 yr; range 59–81 yr) took placebo or DHEA (50 mg/day) for 2 weeks (double blind). After each treatment period subjects participated in an auditory oddball paradigm with three oddball blocks. In the first two blocks subjects had to count the rare tone silently, whereas, in the third block they had to press a button. In addition, memory tests assessing visual, spatial, and semantic memory as well as questionnaires on psychological and physical well-being were presented.

Results. Baseline DHEAS levels were lower compared with young adults. After 2-week DHEA replacement, DHEAS levels rose 5-fold to levels observed in young men. DHEA substitution modulated the P3 component of the ERPs, which reflects information updating in short-term memory. P3 amplitude was increased after DHEA administration, and only selectively in the second oddball block. DHEA did not influence P3 latency. Moreover, DHEA did not enhance memory or mood.

Conclusions. A 2-week DHEA replacement in elderly men results in changes in electrophysiological indices of central nervous system stimulus processing if the task is performed repeatedly. However, these effects do not appear to be strong enough to improve memory or mood.

AGING is accompanied by multiple endocrine changes. One of the most prominent changes is the continued decline of the adrenal steroid hormone dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS (1). Evidence from animal studies has accumulated showing that DHEA and DHEAS can improve memory performance in rodents (2,3) and can enhance hippocampal plasticity (4). In the central nervous system (CNS) DHEAS increases neuronal excitability by acting as a γ -aminobutyric acid receptor type A (GABA_A) antagonist (5) and as a sigma agonist (6). Moreover, in the periphery, the immune-enhancing effects of DHEA have been observed in mice (7) as well as in humans (8).

In respect to cognition in humans, however, an experiment in young subjects did not reveal memory improvement after a single high dose of DHEA (9). A previous 2-week DHEA replacement study (50 mg/day) in elderly women and men from this laboratory could not demonstrate beneficial effects of DHEA substitution on cognition using a battery of neuropsychological tests (10). The latter study also failed to replicate a DHEA-induced increase in well-being as reported in an earlier 3-month replacement study (11).

A sensitive method to assess endocrine effects on the

CNS is to investigate changes in electrophysiological indices of stimulus processing using event-related potentials (ERPs). P300 (or P3), a component that reflects "information updating" in short-term memory (12), has been investigated extensively in gerontological research, and a linear increase in P3 latency with age has been documented. This finding has been interpreted as a sign of "mental slowing" associated with aging. Several reviews have addressed this topic (13–15). For P3 amplitude, a decrease with age is observed (13,16), and there are even more dramatic age-associated changes in P3 amplitude and latency in demented subjects (17,18).

Potentially beneficial effects of vasopressin substitution in elderly subjects have been investigated using ERPs, but no effects on P3 were observed (19). However, a nootropic drug (extracts from the leaves of *Ginkgo biloba*) has been shown to reduce P3 latency in elderly subjects (20). Specific effects of several hormones on ERPs have been investigated in young subjects. Modulatory effects have been observed for peptide hormones [e.g., vasopressin (21)] as well as for cortisol (22). Because DHEA and DHEAS act primarily as GABA_A antagonist in the CNS (5), studies that investigate the effects of drugs acting on the GABA_A receptor complex (e.g., benzodiazepines as GABA agonists) are

especially interesting for the present study. Indeed, several experiments have found decreased P3 amplitude and/or increased P3 latency after benzodiazepine administration (23–25).

In light of these findings, it seemed reasonable to investigate the effects of DHEA replacement on cognition by using ERPs. This approach could be more sensitive to subtle changes induced by the steroid than the broad battery of neuropsychological tests used in the previous study (10). Because with aging P3 latency increases linearly and DHEA concentrations decrease linearly, we hypothesized that DHEA replacement might be able to reverse some of the “mental slowing” obvious in the ERPs. Especially in light of results obtained with GABA agonistic drugs (increased P3 latency and decreased P3 amplitude), DHEAS as a GABA antagonist may have opposite effects. To replicate and extend findings from the previous substitution study (10), memory tests and questionnaires were also employed.

MATERIALS AND METHODS

Subjects

Seventeen healthy elderly men participated in the experiment. Three subjects had to be excluded due to erroneous electroencephalogram (EEG) recordings. The mean age of the remaining 14 subjects was 71.1 ± 1.7 yr (age range, 59–81 yr) with a body mass index (BMI) of 25.2 ± 0.71 (SEM). Nine subjects took medication typically found in an elderly population (mostly hypotensives and cardiac drugs). None of the subjects used a hearing aid. All subjects gave written informed consent and were paid for participation.

Study Design

The study was performed in a double-blind, placebo-controlled crossover design. Two treatment periods of 2 weeks each (placebo or 50 mg/day DHEA) were separated by a 1-week washout period. Half of the subjects received placebo first, whereas the other half received DHEA. Subjects were instructed to take one DHEA or placebo capsule each night at bedtime. Each DHEA capsule (Prasteron, Audor Pharma, Regensburg, Germany) contained 50 mg DHEA and lactose; placebo capsules contained lactose only. Treatment order was randomized. Each subject had four appointments, one before and one after both treatment periods. At each appointment a blood sample was obtained for assessment of DHEAS levels. After both treatment periods, subjects took part in an oddball paradigm (see below). In addition, three questionnaires for the assessment of mood, physical complaints, and perceived changes and three memory tests were used (see below). The experiments took place in the morning (between 8:00 AM and 12:00 PM), and each subject's two test sessions were conducted at the same time of day by the same investigator. The study was approved by the local ethics committee.

Assessment of ERPs

Stimuli and procedure.—An auditory oddball paradigm was used to elicit a P3. The auditory stimuli were high

(1200 Hz) and low (800 Hz) tones delivered via loudspeakers at 70 dB. The interstimulus interval (ISI) was 2 sec. Tones were delivered in a Bernoulli sequence of 80 stimuli. After 80 stimuli had occurred, additional stimuli were presented to obtain a variation in the number of targets in the different series. These additional stimuli were not used for calculation of averages. The probability of occurrence of the rare stimulus was $p = .30$. Subjects had one training trial with 10 stimuli, which was repeated if the subject had problems understanding the task. Three oddball blocks were presented. In the breaks between the oddball blocks, subjects completed questionnaires and participated in memory tests (see below). In the first two oddball blocks subjects were told to count the rare stimulus silently, whereas in the third block they had to press a button as fast and as accurately as possible each time the rare stimulus occurred. The height of the rare stimulus was alternated across the three blocks (the two possible sequences for the rare tone were high-low-high or low-high-low).

Recording and data analysis.—The EEG was measured from nine locations (F4, C4, P4, Fz, Cz, Pz, F3, C3, and P3). Horizontal and vertical electrooculograms (EOGs) were measured to control for ocular artifacts. The ECI-Electrocap system (Electro-Cap International, Inc., Nieuwkoop, The Netherlands) with embedded tin electrodes was used. Before placement of the cap, the expected electrode sites were cleaned with alcohol and gently abraded. Interelectrode impedance was always below 3000 Ω and often below 1000 Ω . EEG and EOG were amplified with a Nihon-Kohden 4314 G amplifier (Bad Homburg, Germany). The time constant was set to 10 sec, and the high pass filter was set at 35 Hz. The EEG and EOG were digitized from 200 msec prestimulus to 1200 msec post-stimulus, with a sample rate of 100 Hz. Prior to averaging, horizontal and vertical EOG was removed from the EEG by using an algorithm proposed by Gratton et al. (26) and extended by Miller et al. (27). Trials containing severe amplifier drifts or muscle artifacts were excluded from averaging (this was the case for less than 1%). At each electrode site, averages were computed for rare and frequent oddball stimuli in each of the three blocks. P3 was defined as the most positive peak in the time region between 260 and 600 msec at Pz. At all other locations the latency and peak measurement were determined with reference to the latency at Pz.

Psychological assessment.—Three questionnaires were used for the assessment of mood, self-perceived changes, and physical complaints.

- (i) Mood questionnaire: In the multidimensional mood scale adjectives are presented that describe mood states on three scales: elevated versus depressed mood, wakefulness versus sleepiness, and calmness versus restlessness (28).
- (ii) Rating of self-perceived changes: Subjects were asked whether they had experienced changes during the last 2 weeks in six different domains (contentment, sleep quality, sexual desire, pain, activity, concentration).

Subjects had to indicate changes on a 5-point scale.

- (iii) Physical complaint questionnaire: Subjects had to rate physical complaints according to the intensity with which they experienced them. Five scales are generated: sleep problems, cardiac and blood pressure problems, gastrointestinal problems, tension, and pain (29).
- (iv) Unstructured interview: In addition to the questionnaires, subjects were asked if they had perceived any psychological or physical changes during each treatment period.

Memory Tests

Three memory tests were selected. Visual memory was again assessed to compare results of the present experiment with previous results from this laboratory (10). Two additional memory tests were used (spatial and semantic memory) because specific effects of bioactive sex steroid hormones (testosterone and estradiol) on these memory domains have been demonstrated (for review, see ref. 30).

Visual memory (picture memory test).—Fourteen pictures showing everyday objects (e.g., fruits, clothes) were presented at a rate of one picture every 2 sec. The subject had to name each object shown in order to assure the researcher that the object was recognized correctly. Immediate and delayed (after the second oddball block) free recall were assessed (31).

Spatial memory (city map test).—Subjects were asked to memorize (within 2 min) a route marked on a city map. Immediately thereafter subjects had to draw the learned route onto an unmarked map. Number of correctly chosen roads (maximum of 31) was determined and used as test score (32).

Semantic memory (verbal fluency).—Subjects had to produce verbally as many words as possible within a given first letter (B or D; open category) or within a given category (fruits or vegetables; closed category) in 1 min. In the letter condition, only nouns, adjectives, and verbs were allowed. Order-of-category conditions were randomized between subjects. Words were taped, and the number of correctly produced words was used as the test score.

Hormone Assays

Plasma DHEAS levels were measured at all four appointments. A commercially available assay was used (ELISA; IBL, Hamburg, Germany). The sensitivity of this assay is .05 µg/ml. The inter- and intraassay coefficients of variations are 7% and 8%, respectively.

Statistical Analyses

Hormone data were analyzed with an analysis of variance (ANOVA) with one factor sampling period (four levels). For ERPs, ANOVAs were calculated only in respect to those electrodes at which a particular component displayed its maximum amplitude (which was Pz for P3, Cz for P2, and Fz for N1). Separate ANOVAs were performed for the first two blocks (counting instruction) and the third block (button pressing). Three additional subjects had to be

excluded for analysis of the third block because they pressed the button at one (two subjects) or both (one subject) test sessions in response to the frequent tone. Post hoc comparisons were performed by using the Newman-Keuls test. The two standardized questionnaires were analyzed with an ANOVA with the factors "treatment" and "questionnaire scale." Data from the self-perceived changes rating scale were analyzed by using the Wilcoxon matched pairs test for each of the six domains separately. Memory data were analyzed with Student's *t* test.

RESULTS

DHEAS

DHEAS baseline levels ($.82 \pm .16$ µg/ml) were significantly lower when compared to levels reported in young men, who have DHEAS levels between 3 and 4 µg/ml. ANOVA indicated a significant effect of sampling time [$F(1,39) = 66.8, p < .0001$]. Post hoc testing revealed that DHEAS levels after DHEA treatment were significantly higher than at the other three sampling points (all $p < .001$). There was no difference between baseline, placebo, or washout DHEAS levels (Figure 1).

Event-Related Oddball Potentials

The grand means for the rare tone in the first two oddball blocks are presented in Figure 2.

P3 amplitude.—The three-way ANOVA (treatment, oddball, blocks) revealed, as expected, a significant main effect of oddball [$F(1,13) = 42.57, p < .0001$]. There was no main effect of treatment, [$F(1,13) = 0.63, p = .44$] but there was a significant treatment by block interaction [$F(1,13) = 7.03, p < .05$]. Although DHEA-treated subjects did not differ significantly from subjects under placebo in the first oddball block, they showed a significantly larger amplitude ($p < .05$) in the second block (Figure 3). In addition, a close to

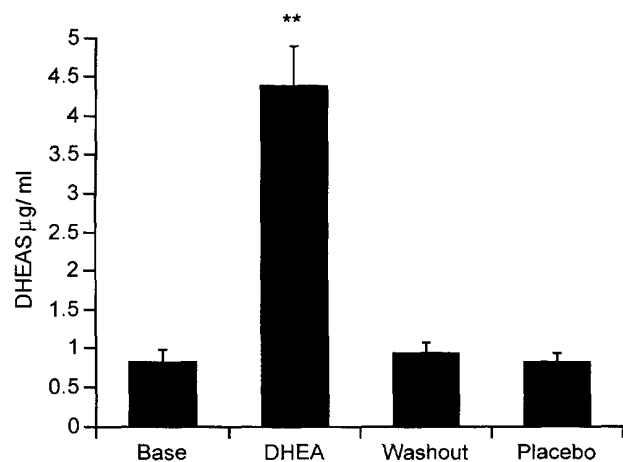


Figure 1. DHEAS levels during the course of the experiment. (Note: treatment order was randomized and counterbalanced, but for easier reading data are presented as if all subjects had DHEA first.)

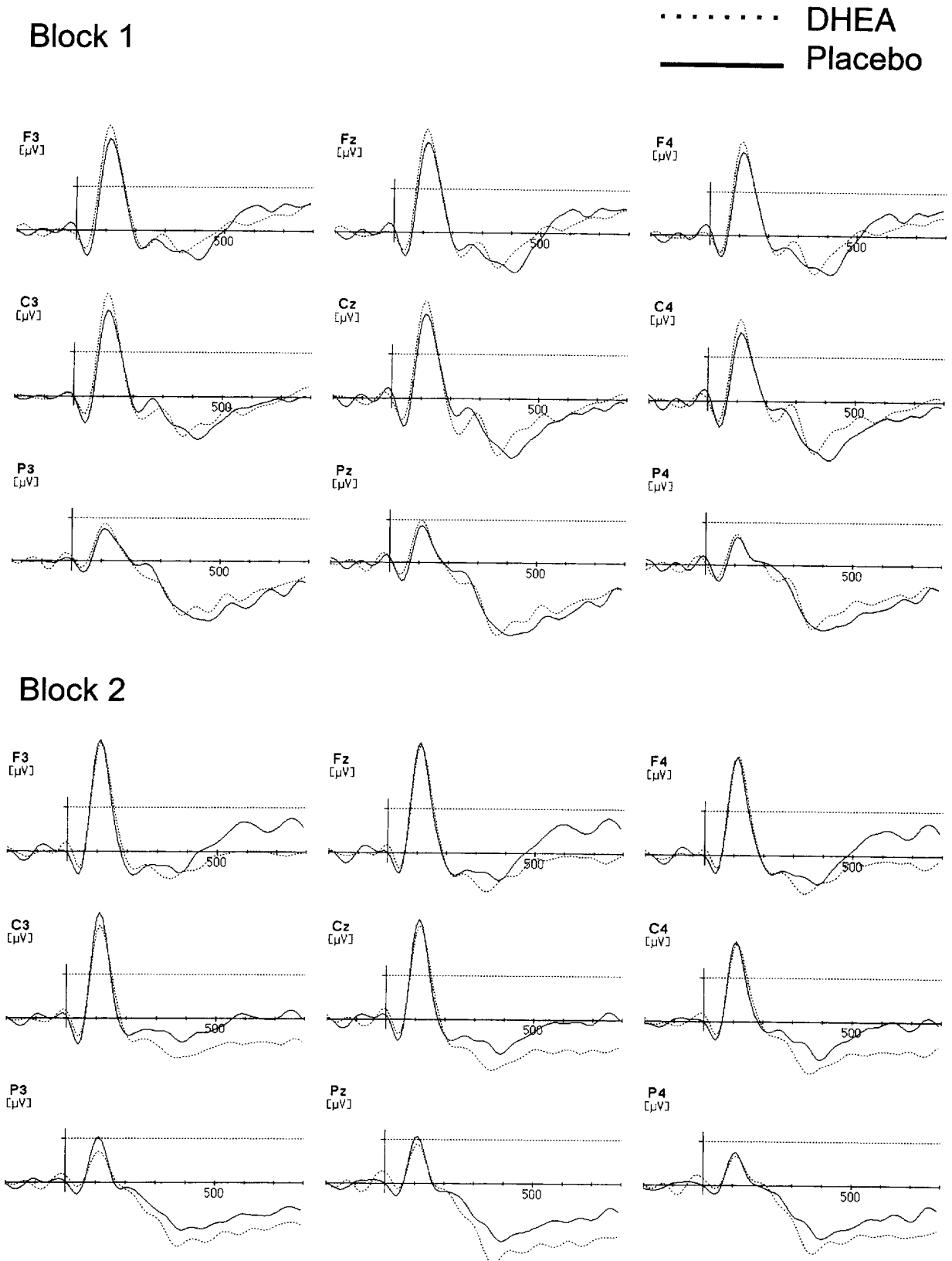


Figure 2. Grand means of responses to the rare target tone from subjects under DHEA or placebo in two oddball blocks, which were separated by a 10-min break. In both blocks subjects had to count the rare tone silently. Scale of the x-axis in msec; dotted line on the y-axis indicates 5 μV .

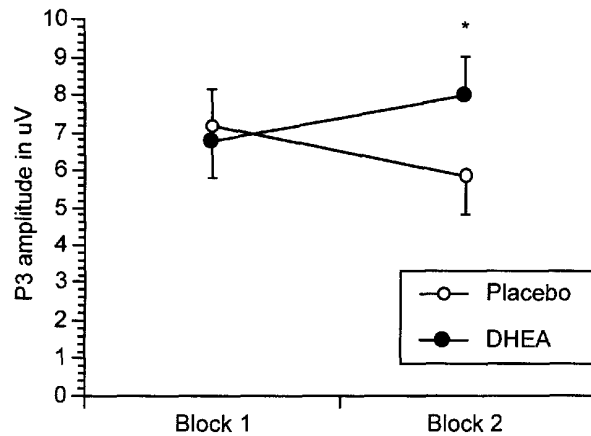


Figure 3. Effects of DHEA on P3 amplitude in the two oddball blocks. In both blocks the subjects had to count the rare tone silently.

significant [$F(1,13) = 3.76, p = .07$] treatment by block by oddball interaction was detected, which indicated that the enhanced P3 amplitude under DHEA in the second block tended to be more pronounced in response to the rare tone.

Evaluation of DHEA effects on P3 amplitude in the third oddball block (pressing instruction) revealed neither a main effect of treatment (P3 amplitude: $8.9 \pm 1.5 \mu\text{V}$ under placebo vs $8.5 \pm 2.4 \mu\text{V}$ under DHEA) nor a treatment by oddball interaction ($p > .10$ for both comparisons).

P3 latency.—The same ANOVA model was used for analysis of DHEA effects on P3 latency in the first two blocks. There was neither a main effect of treatment (395.0 ± 10.0 msec under placebo vs 389.5 ± 11.8 msec under DHEA) nor a treatment by oddball or treatment by block interaction (all $F < 1$). DHEA also had no significant effects on P3 latency in the third block.

P2 and N1.—No significant differences between DHEA and placebo could be detected for P2 and N1 latency as well as amplitude in any of the three oddball blocks.

Mood, Physical Complaints, and Self-Perceived Changes

ANOVA of the mood data showed neither a significant treatment main effect [$F(1,13) < 1$] nor a significant treatment by scale interaction [$F(2,26) < 1$]. DHEA also did not influence self-perceived changes in the two treatment periods ($p > .20$ for all six comparisons). There was also no significant effect of the hormone on the amount of reported complaints. In the unstructured interview only a small number of changes were reported. Three subjects reported changes after DHEA, which consisted of two positive (reduced pain, more active) changes and one negative (more forgetful) change. Under placebo, three negative (mild flu, reduced sleep, and reduced sexual desire) changes and one positive (more active) change were reported. The only subject who rated his changes as marked was the one who reported reduced sleep quality and reduced sexual desire under placebo.

Table 1. Performance in Three Memory Tests After DHEA or Placebo Treatment

	Placebo	DHEA	t-value	p-level
Visual memory				
Immediate recall	8.0 ± 0.4	8.1 ± 0.6	0.4	NS
Delayed recall	6.8 ± 0.5	6.6 ± 0.8	0.6	NS
Spatial memory				
Correct decisions (maximum 31)	15.7 ± 1.5	16.7 ± 1.4	0.8	NS
Semantic memory				
Open category	13.5 ± 0.8	13.8 ± 1.4	0.2	NS
Closed category	11.6 ± 1.1	12.7 ± 0.6	0.8	NS

Note: Data are given as mean \pm SEM. NS, not significant.

Memory Performance

DHEA also did not influence memory performance in three different tests (Table 1). No trend was obvious, even without alpha adjustment for multiple comparisons.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the effects of a physiological DHEA replacement on CNS stimulus processing using ERPs. The main finding was a significantly enhanced P3 amplitude under DHEA in the second oddball block (counting instruction). No such difference was observed in the first (also counting instruction) or in the third (button pressing) block. This significant P3 amplitude enhancement is the first electrophysiological evidence that DHEA replacement might have some positive effects on CNS functioning. Whether these effects are restricted to DHEA-deficient elderly individuals or they can also be observed in younger subjects remains to be tested. No treatment effects were obtained for P3 latency or for earlier ERP components (P2 and N1). The failure of DHEA to shorten P3 latency indicates that a 2-week replacement does not increase speed of information processing in short-term memory. Although no young control group participated in the experiment, the P3 latency of the elderly subjects (≈ 390 msec) was enhanced when compared to reference values of younger subjects as provided in Polich (15). At least this comparison with normative data argues against a possible ceiling effect in this population of healthy elderly men.

Several reasons may account for the selective P3 amplitude increase during the second performance of the task. One possibility is that the subjects first had to become familiar with the task and the laboratory setting. However, the fact that in the third block (manual response) no DHEA effects were observed argues against a rather nonspecific influence of novelty on the DHEA effects on P3 amplitude. Because only one block with button pressing had to be performed, it remains open whether a P3 amplitude increase would also occur with repeated task performance. From a neurobiological perspective, an alternative explanation could be that the specific neuronal pathways that are involved in the task performance first have to be primed or strengthened before enhancing effects of DHEA can be

observed. Of course, the findings could also be interpreted as nonhabituation or as a DHEA-reduced tiredness in response to the simple but probably still exhausting task. However, at least in the questionnaire, no increased wakefulness was reported.

The effects of DHEA on ERPs were not accompanied by positive effects of the steroid on performance in the memory tasks. However, although some studies report an association between P3 data and behavioral indices (33,34), other studies documented specific effects on P3 that were not paralleled by behavioral changes (23,24).

The use of a semantic and a spatial memory task, two skills that are both sensitive to the influence of bioactive sex steroids such as estradiol and testosterone (30), extends the negative findings from the first DHEA replacement study from this laboratory (10) to these memory types. In the questionnaires about mood, perceived changes, and physical complaints, again no beneficial effects of DHEA could be observed, which replicates previous findings (10). In addition, in the open interview, only 2 of 14 subjects reported positive changes under DHEA.

Taken together, the present findings demonstrate subtle effects of DHEA replacement on CNS stimulus processing in an oddball paradigm when the task is presented for the second time. This is the first evidence that oral DHEA replacement can indeed positively modulate CNS functioning in elderly humans. However, because the observed beneficial effects on P3 amplitude appeared only under specific circumstances and were not accompanied by desirable changes in memory performance or mood, this study again does not support the idea of strong positive effects of DHEA replacement in this population. However, longer DHEA replacement or DHEA administration to elderly subjects with impaired cognition may lead to more favorable results.

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