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OPPOSING EFFECTS OF DHEA REPLACEMENT IN ELDERLY SUBJECTS ON DECLARATIVE MEMORY AND ATTENTION AFTER EXPOSURE TO A LABORATORY STRESSOR

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SUMMARY

Aging is accompanied by a continuous decline of the adrenal steroid hormone DHEA and its ester DHEAS. Results from studies in rodents have demonstrated that DHEA(S) administration can enhance memory in several test paradigms. However studies from this laboratory did not find positive effects of DHEA treatment on cognitive performance in young and elderly humans. With respect to a possible mechanism of DHEA activity, effects on several neurotransmitter receptors as well as a possible antiglucocorticoid action are discussed. For high levels of glucocorticoids, a disruptive effect on hippocampal mediated memory is documented in rodents and humans. Therefore it was speculated that, if an antiglucocorticoid action of DHEA would underlie the observed beneficial effects of DHEA on memory, these effects might only be detectable if subjects are stressed (and therefore have high cortisol levels). To test this hypothesis 75 elderly women and men participated in a placebo controlled experiment. Subjects took DHEA (50 mg/day) or placebo for 2 weeks (double blind). Thereafter they participated in a standardized psychosocial laboratory stressor (Trier Social Stress Test; TSST). Before and after stress exposure subjects completed two declarative memory tests (visual–verbal and spatial) as well as one attention test. In addition recall of visual material learned before stress was assessed after stress. Baseline DHEAS levels were significantly lower compared with young adults. DHEA replacement increased DHEAS levels into ranges found in young subjects. DHEA-substituted subjects showed a trend towards a larger cortisol stress response. In the visual memory test subjects under DHEA recalled less items after stress which they had learned before stress. In the attention test however subjects under DHEA performed better than subjects from the placebo group after stress. No interaction between stress and DHEA was found for the spatial memory task. The effects of DHEA substitution on memory and attention after stress exposure seem to be heterogenous. While recall of previously learned material seems to be impaired, attention is enhanced. These results do not support the idea of a direct antiglucocorticoid or anti-stress effect of DHEA on hippocampal mediated memory functions. ©1998 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

Aging is accompanied by a continuous decline of the adrenal steroid DHEA and its sulfate ester DHEAS, which is the most abundant steroid hormone in man (Orentreich et al., 1984). Animal studies have demonstrated that DHEA(S) has antiamnestic as well as memory enhancing properties in a foot shock avoidance paradigm (Flood et al., 1988), in a working memory task (Melchior and Ritzmann, 1996), and in the morris watermaze (Frye and Sturgis, 1995). However a recent study reported impaired contextual fear conditioning after DHEAS treatment (Fleshner et al., 1997). In addition DHEAS enhances neuronal plasticity in the hippocampus (Diamond et al., 1996a). These effects may be mediated by the known antagonistic action of DHEA(S) on the GABA-A receptor (Majewska, 1992) and agonistic action on the sigma receptor (Monnet et al., 1995). The hypothesis that DHEA may also increase cognitive performance in humans could not be supported by findings from this laboratory. In a first study no beneficial effect of a single DHEA administration on memory in young subjects was observed (Wolf et al., 1997a). In elderly subjects a 2 week physiological DHEA replacement (50 mg/day) had no effects on performance in several neuropsychological tests (Wolf et al., 1997b). However subtle central effects of DHEA replacement could be detected in the EEG during an oddball paradigm (Wolf et al., in press). In this experiment DHEA replaced subjects showed an enhanced P3 amplitude under certain conditions.

In addition to the discussed neuroactive action of DHEA in the rodent CNS immunological studies have suggested that DHEA might exert antiglucocorticoid effects. Several studies observed that DHEA treatment reversed the stress or glucocorticoid induced suppression of the immune system (Kalimi et al., 1994). However the mechanism of this effect is still poorly understood, therefore DHEA is often termed a 'functional antiglucocorticoid'.

With respect to the effects of glucocorticoids on memory, experimental studies in humans and animals have shown that high levels of GCs impair memory. Several recent reviews have addressed this topic (Lupien and McEwen, 1997; McEwen and Sapolsky, 1995; Wolf et al., 1998). In humans experimental studies have shown that administration of dexamethasone (Newcomer et al., 1994) or cortisol (Kirschbaum et al., 1996) selectively impaired declarative memory functions. While declarative memory is dependent on an intact hippocampal formation, other memory forms (procedural or non-declarative) seem not to rely on the hippocampus (Eichenbaum et al., 1992; Squire, 1992). The selective GC induced impairment of hippocampal processed memory fits to the observation that the hippocampus is the brain structure with the highest receptor density for GCs (Jacobson and Sapolsky, 1991). High circulating levels of GCs lead to an enhanced occupation of the type II receptors, or GRs, which are only minimally occupied under basal conditions. The type I receptor, or MR, is already heavily occupied under basal conditions since its affinity for cortisol is 10-fold higher than that of the GR (de Kloet et al., 1993). Electrophysiological studies in rodents revealed that the MR enhances neuronal plasticity in the hippocampus as indicated by increased LTP while the GR has opposing effects on LTP (Pavlides et al., 1995).

Therefore it is not surprising that animal studies have shown that stress blocks hippocampal plasticity and impairs declarative memory (Diamond and Rose, 1994; McEwen and Sapolsky, 1995). A study from this laboratory in humans found a negative correlation between the cortisol increase in response to a psychosocial stressor and the amount of correctly recalled words in a declarative memory test after cessation of stress (Kirschbaum et al., 1996), i.e. subjects with a marked cortisol response performed poorer in the memory task. In line with this observations a recent study carried out by Lupien and coworkers reported evidence that stress impaired declarative but not procedural memory performance in healthy elderly subjects (Lupien et al., 1997).

Taken together there is good evidence that stress- or pharmacologically-induced elevation of GC levels impairs hippocampal dependent memory. If some of the memory enhancing effects of DHEA are due to its presumed antiglucocorticoid actions, then one might speculate that this effect becomes most obvious if subjects are stressed showing high GCs levels.

The present research project focused on: (a) endocrine and cardiovascular stress responses and its modulation by a DHEA treatment in elderly subjects; and (b) the effects of DHEA replacement on declarative memory and selective attention before and after stress exposure. Results on the first part of the project are provided in Kudielka et al. (1998).

Regarding the second part reported here, the hypothesis outlined above would predict that subjects under DHEA perform better in the declarative memory test than subjects under placebo after stress exposure only. This effect should be specific to declarative memory and should not be apparent in other cognitive tests (e.g. the attention task).

METHODS

Subjects

Thirty-seven women with a mean age of 67.4 ± 0.8 (SEM) years (range 60–77) and a body mass index (BMI) of 25.5 ± 0.6 and 38 men with a mean age of 67.5 ± 0.9 years (range 59–81) and a BMI of 25.8 ± 0.4 volunteered to participate in the present experiment. Initially 81 subjects were recruited, but three subjects were excluded due to high depression scores and another three subjects did not participate in the memory tests for various reasons. Hence a cognitive data set was available from a total of 75 subjects. On a first appointment in the research center, subjects were medically screened by a physician with special emphasis on cardiaovascular and endocrine disorders in order to assure that stress exposure will not lead to medical complications. None of the subjects had serious memory complaints. Some subjects took medication typically found in an elderly population (cardiac drugs, hypotensives, adrenergics etc.). Subjects were recruited via the local newspaper or by phone and were paid for participation. Subjects were told that they had to give a public speech on the second appointment and that cognitive performance would be tested before and after this. All subjects gave written informed consent. The study protocol was approved by the ethics committee of the University of Trier.

Study Design

A double blind group comparison design was chosen. Approximately one half of the subjects were randomly assigned to received DHEA for 2 weeks whereas the other half

received placebo. The DHEA group contained 42 subjects (22 men and 20 women), whereas the placebo group contained 33 subjects (16 men and 17 women). The two groups were matched for age and BMI. Subjects were instructed to ingest one DHEA or placebo capsule each night at bed time. One DHEA capsule (Prasteron, Audor Pharma, Regensburg, Germany) contained 50 mg DHEA and lactose; placebo capsules contained lactose only. After the 2 week treatment period subjects came to the laboratory between 0900 and 1000h. They completed tests on cognitive performance and participated in a psychosocial stress test. Cognitive testing was done before stress exposure (40 min before) and 10 min after cessation of stress. Three tasks were used for the assessment of memory and attention (see below). Cognitive testing lasted for ~ 15 min. Parallel versions of the tasks were used at the two test sessions and the order of the parallel versions was randomized. A schematic outline of the experimental protocol is given in Fig. 1.

Assessment of Cognitive Performance

Parallel versions of the following tests were presented to the subject before and after exposure to the laboratory stressor.

Visual–verbal Memory (Oswald and Fleischmann, 1994). Fourteen pictures showing everyday objects (e.g. fruits, clothes) were presented at a rate of one picture every 2 s. The subject had to name each object aloud in order to assure that the object was recognized correctly. Delayed free recall was tested after completion of the attention test (see below) ~ 2 min later. Delayed recall was assessed in order to measure hippocampal dependent memory processes (Squire, 1992). In addition recall of pictures learned before stress exposure, was tested after stress exposure.

Selective-attention (Gatterer, 1990). On a piece of paper the subject had to cross out a specified target item (a half-circle) out of several similar looking distractor items

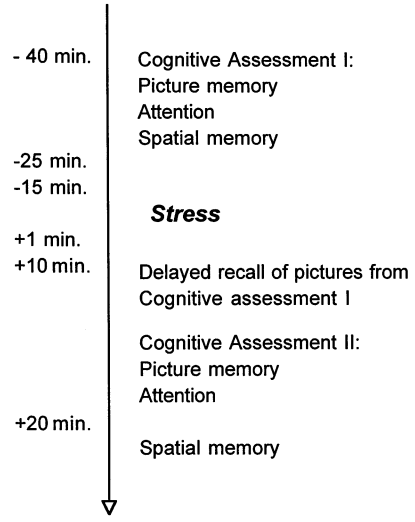

Fig. 1. Time-line of the experimental protocol.

(half-circles which differ in color and/or position). Time for completion, as well as the number of correct decisions (correct positive: max. 20), and the number of errors (false positive) were measured. A performance score was computed by subtracting the amount of errors from the amount of correct decision. This variable was used as the dependent variable.

Spatial Memory. A 'mental rotation' task was used to assess spatial memory. This test is a modified version of a task described by Franklin et al. (1992) and adapted by our laboratory in an attempt to assess spatial memory with a paper and pencil test (Kirschbaum et al., 1996). In this task the subject first read a description of a scene in a room (a barn or a museum) with seven objects located around them. Two minutes time to memorize the location of the objects were allowed. Thereafter two test sheets were handed out. In the first one the subject had to indicate the location of the objects (with multiple choice tasks being used). On the second test sheet the subject had to indicate the location of the objects after an imaginary 90° rotation (again with multiple choice questions being used). Prior studies have shown that this task is sensitive for GC induced declarative memory impairments (Kirschbaum et al., 1996).

Stress Paradigm

The 'Trier Social Stress Test' (TSST) was used (Kirschbaum et al., 1993). This standardized laboratory stressor consists mainly of a free speech (5 min) and mental arithmetics (5 min) in front of an audience.

Saliva and Blood Sampling

At both appointments at the research center, a blood sample was taken for the determination of DHEAS levels. At the test day saliva samples for the analysis of free cortisol levels were collected by the subjects 15 min before and 1, 10, 20, min after stress using Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Samples were stored at -20°C until biochemical analysis.

Hormone Assays

DHEAS plasma levels were measured using a commercially available assay (ELISA; IBL, Hamburg, Germany). The inter- and intraassay coefficients of variations were below 10%. Saliva cortisol was determined using an immunoassay with a biotin cortisol tracer, streptavidin–europium label, and a time resolved fluorescence detection system (DELFIA; Dressendörfer et al., 1992). Intraassay as well as interassay coefficients of variation were below 10%.

Statistical Analysis

Normal distribution of the dependent variables was confirmed using Kolmogorov–Smirnov test. ANOVAs with the two independent factors sex and treatment were calculated for analysis of the endocrine as well as cognitive data. Post hoc testing was carried out using Tuckey tests. In addition Spearman Rank correlations were computed between delta scores from endocrine and cognitive data.

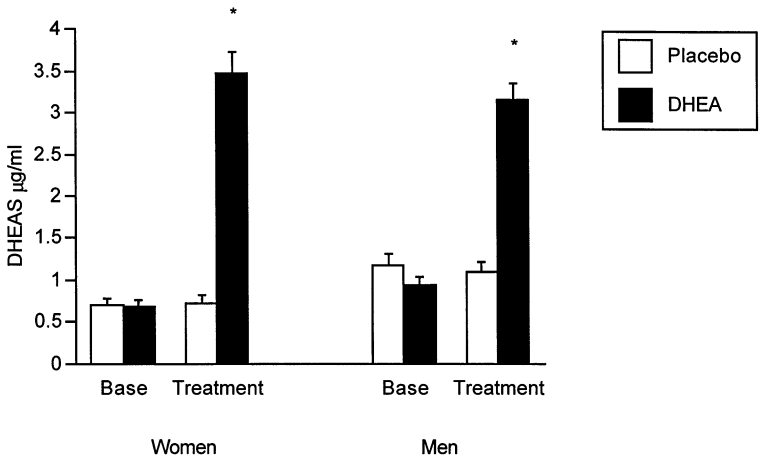

Fig. 2. DHEAS levels of the subjects after 2 weeks of DHEA or placebo treatment.

RESULTS

Subject Characteristics

Student's t-test results showed that the two treatment groups did not differ with respect to age ($t(73) = -.63$; $p > .15$) or BMI ($t(73) = 1.43$; $p > .15$).

Endocrine Effects

Only the endocrine changes relevant for evaluation of the cognitive effects are presented here. More detailed information on pituitary–adrenal and cardiovascular responses to DHEA treatment and psychosocial stress are reported elsewhere (Kudielka et al., 1998). Because cognitive testing was finished ~ 25 min after stress exposure, only data of this time window are included in the present analyses.

Two weeks of DHEA treatment resulted in a significant rise in DHEAS levels in women and men, no changes were seen in the placebo group of either sex (Fig. 2). A three-way ANOVA (sex, treatment, time) indicated a significant treatment by time interaction ($F(1, 71) = 204$; $p < .0001$). DHEA treatment led to a 4-fold increase in DHEAS levels, while placebo treatment had no effects on DHEAS levels. The mean levels of DHEA replaced subjects were in the upper reference levels of young adults (Orentreich et al., 1984).

The effects of DHEA treatment on stress induced cortisol secretion were evaluated with a three-way ANOVA (sex, treatment, time). Four cortisol measurements (-15 min to $+20$ min) were included in the analysis since only this time window was of relevance for the following evaluation of the cognitive data. ANOVA indicated a significant main effect of time ($F(3, 210) = 35.3$; $p < .0001$), showing that the stress paradigm increased free cortisol levels. In addition, a trend towards a main effect of sex ($F(1, 70) = 2.76$; $p = .10$) was observed with men having higher cortisol levels than women. Moreover, there was a close to significant group by time interaction ($F(3, 210) = 2.11$; $p = .09$). Subjects under DHEA tended to show a more pronounced cortisol increase in response to the TSST (Fig. 3).

Fig. 3. Cortisol levels in response to the TSST of subjects after 2 weeks of DHEA or placebo treatment.

Cognitive Effects

Visual–verbal Memory. First the effects of DHEA substitution and stress on recall of previously learned material was evaluated (pictures presented before stress). A three-way ANOVA was computed with the main effects sex, treatment, and the repeated measurement factor 'stress' (recall before and after stress). There was no main effect of sex ($F(1, 71) = 0.2$) or treatment ($F(1, 71) = 1.1$), but a significant main effect of stress ($F(1, 71) = 29.00$; $p < .0001$). After the stressor subjects recalled less items learned before stress exposure. In addition, there was a significant sex by stress interaction ($F(1, 71) = 4.2$; $p < .05$). Post hoc testing revealed that women recalled significantly less items after stress ($p < .01$) than before stress, while there was only a trend for such stress effect in men ($p = .10$). While women tended to perform better than men in their recall before stress ($p = .09$) but they did not differ from men after stress ($p = .94$; Fig. 4).

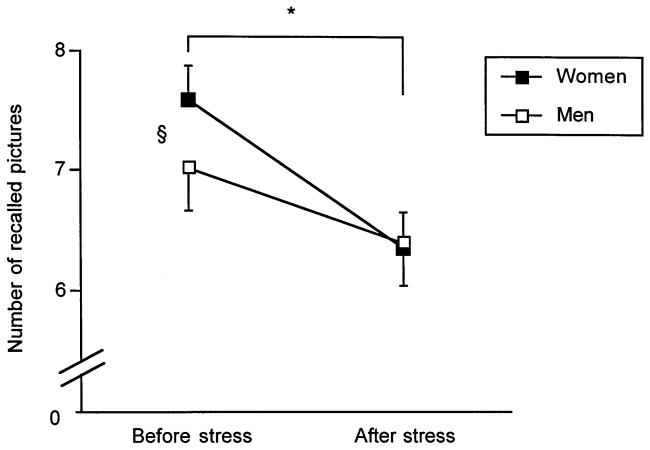

Fig. 4. Effects of gender and stress on recall of material learned before stress (recall was tested twice once before and once after stress exposure). * $p < .05$ between pre- and post-stress recall (women). § $p < .10$ between men and women.

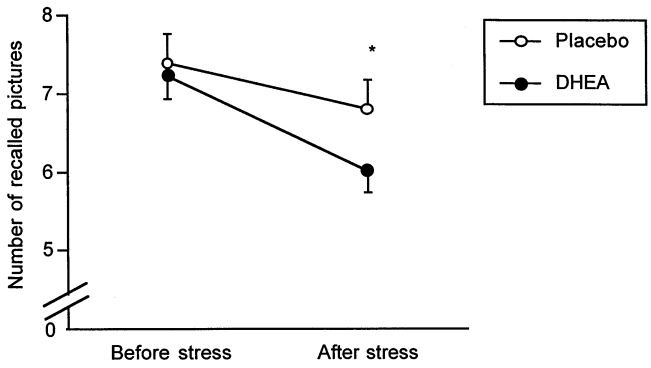

Fig. 5. Effects of DHEA and stress on recall of material learned before stress (recall was tested twice: once before and once after stress exposure). * $p < .05$ between DHEA and placebo.

The treatment by stress interaction was also significant ($F(1, 71) = 3.99$; $p < .05$). Post hoc testing revealed that while subjects under DHEA did not differ in their recall performance before stress ($p = .57$), they performed significantly poorer than subjects under placebo if recall was tested after stress exposure ($p < .01$; Fig. 5). The three-way interaction (sex by treatment by recall condition) was not significant ($F(1, 71) = 0.93$).

A second analysis was computed to compare performance in the picture memory test before and after stress. Recall of material learned and recalled before stress was compared with recall of material learned and tested after stress. Again there was no main effect of sex ($F(1, 71) = 1.47$; $p = .23$) or treatment ($F(1, 71) = 0.13$) but a significant effect of stress ($F(1, 71) = 4.26$; $p < .05$). Performance of the whole group was poorer after stress. None of the further interactions (two- or three-way) were significant (all $p > .05$).

Selective-attention. One subject from the placebo group committed a systematic error due to a misunderstanding of the task instruction. Therefore he had to be excluded from the analysis. First, the time needed for completion of the task was evaluated. A three-way ANOVA was computed (group, sex, stress). Neither main effect of sex ($F(1, 70) = 0.3$) nor treatment ($F(1, 70) = 1.6$; $p = .21$) were significant but there was a significant main effect of stress ($F(1, 70) = 20.56$, $p < .001$). The time needed for completion of the task increased form 33.7 ± 1.1 s before stress to 37.9 ± 1.1 s after stress. None of the further interactions (two- or three-way) became significant (all $p > .05$).

The performance score was analyzed with the same ANOVA model. There was no main effect of sex or treatment (both $F < 1$) but a trend towards a main effect of stress ($F(1, 70) = 2.8$; $p = .10$). In addition there was a significant treatment by stress interaction ($F(1, 70) = 7.3$; $p < .01$). While the performance decreased significantly after stress in the placebo group ($p < .05$), this was not the case in the DHEA group ($p = .85$). As a consequence, the placebo group tended to perform poorer than the DHEA group after stress ($p = .056$) while there had been no difference in performance between the groups before stress exposure ($p = .59$; Fig. 6). None of the other interactions became significant (all $p > .20$).

Kolmogorov–Smirnov test indicated that the performance variable was not normally distributed, therefore the treatment by stress interaction was evaluated with a nonparametric test (U-test). Here, the performance delta values were used as the dependent variable. Again a significant difference between the two groups was observed ($Z = -2.15$; $p < .05$).

Spatial Memory. Another subject from the placebo group failed to understand the task instructions and did not memorize the location of the objects (but only memorized the objects). Therefore he had to be excluded from the analysis of this task. Effects of DHEA and stress on the spatial memory task were evaluated with a four-way ANOVA (sex, treatment, stress, task (with and without mental rotation). Neither the treatment main effect nor any of the possible treatment interactions were significant (all $p > .05$). Therefore the results of this task are described very briefly. There was a main effect of sex ($F(1, 70) = 7.1$; $p < .01$) with men committing significantly fewer errors than women (total number of errors: 10.1 ± 0.9 for men and 13.6 ± 0.9 for women). There was also a significant main effect of stress ($F(1, 70) = 5.4$; $p < .05$). Subjects committed less errors after stress probably indicating a practice effect. As expected there was also a significant main effect of task ($F(1, 70) = 36$; $p < .001$). Subjects committed more errors in the second task (with mental rotation).

Associations between Cognitive Performance and Cortisol Response. In addition to the group comparisons associations between cortisol responses to the TSST and cognitive performance after stress exposure were evaluated. Delta variables for the cortisol increase (10 min after stress minus 15 min before) as well as for the change in cognitive performance after stress were computed (post-stress minus pre-stress test score). There was a trend towards an association between a decreased performance in the picture memory test (performance in the picture memory test after stress minus performance in the picture memory test before stress) and a higher cortisol increase in response to the TSST ($r = -.20$; $p = .10$), but their was no association between the cortisol response and recall of the first set after stress (recall of the first set after stress minus recall of the first set before stress). A second trend indicated that subjects with a more pronounced cortisol rise needed more time for completion of the attention test ($r = .20$; $p = .09$). However, these two correlations explained only 4% of the variance. No additional significant correlations were observed if the analysis was carried out for women and men, or for DHEA or placebo treated subjects separately.

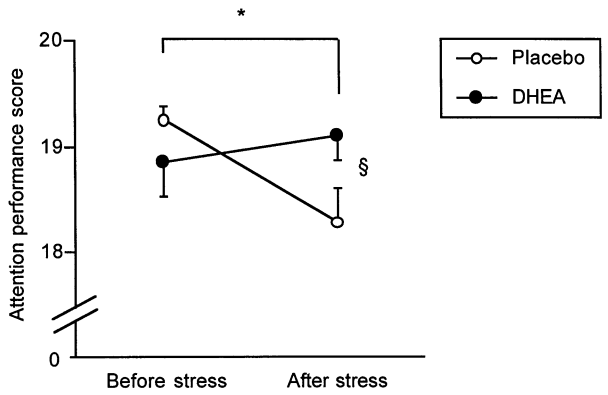

Fig. 6. Effects of DHEA and stress on performance in an attention test. Performance (using parallel versions) was tested before and after stress, respectively. * $p < .05$ between pre- and post-stress performance (placebo). § $p < .10$ between DHEA and placebo.

DISCUSSION

The present study set out to test the hypothesis that an antiglucocorticoid action of DHEA would result in an enhanced declarative memory performance in DHEA treated subjects after stress-exposure. The results obtained in this study do not support this idea. DHEA treated subjects recalled less items after stress from a visual memory test. Since in other studies no impairing effect of DHEA on visual long-term retention was observed (Wolf et al., 1997b; in press), the explanation that a DHEA by stress interaction is responsible for the obtained results seems justified. One possible reason for this effect might be the trend towards an enhanced free cortisol stress response in DHEA treated subjects. One problem with this interpretation however is that recall performance was not correlated with the cortisol increase, indicating that there was no linear association between these two variables. An additional complication arises from the fact that women who had lower cortisol levels forgot more items which they had learned before stress. One explanation for this sex differences could be that on a rating scale women indicated that they were more stressed than men, suggesting that psychological rather than endocrinological effects might best explain this finding (Kudielka et al., 1998). However it might also be possible that women are more susceptible to the memory impairing effects of GCs. In line with this hypothesis is a recent report which demonstrated that in elderly women but not men higher basal cortisol levels were associated with poorer memory (Seeman et al., 1997). Previous studies, which investigated the effects of stress on cognition in humans included not enough subjects to detect sex differences (Kirschbaum et al., 1996; Lupien et al., 1997).

While the two treatment groups differed significantly in the recall task, differences in performance in the visual task were neither detected before nor after stress. There is animal literature suggesting that stress causes only a retrograde amnesia while it does not interfere with test-performance after stress exposure (Diamond et al., 1996b). A previous study which investigated the effects of stress on memory in elderly humans tested recall (and not performance) after stress exposure (Lupien et al., 1997).

It has to be mentioned, that the 2 min delay between picture presentation and first recall test used in this study might not have been long enough in order to rule out a possible contribution of working memory to the performance. Working memory which is not dependent on the hippocampus (Squire, 1992) and it seems not to be impaired by glucocorticoids (Fehm-Wolfsdorf et al., 1993). However, the attention test used which had to be carried out between learning and recall should have occupied most of the working memory capacity.

The decreased performance of the total group in the picture memory test after stress exposure suggests that stress does indeed also impair performance after stress. However since no control group (without stress exposure) was available in this study, alternative explanations for the poorer performance after stress can not be ruled out (e.g. proactive interference from the first test, increased fatigue, decreased motivation).

While the results of the visual memory test do not point to a beneficial effect of DHEA replacement on cognitive performance after stress, a different picture emerged in the attention test. Here DHEA treated subjects did not show a decrease in their performance after stress while subjects under placebo did (although they still performed close to maximum). Therefore, they tended to perform better than subjects under placebo after stress. The question whether the results reflect a specific DHEA by stress interaction or rather are the cause of a DHEA by repeated task presentation interaction can not be

answered with the available data. No comparison with an unstressed control group is possible here and in an earlier DHEA replacement study the task was only presented once (Wolf et al., 1997b). However, one experiment reported that cortisol administration enhanced attention and activation as assessed by questionnaire (Plihal et al., 1996). The latter finding might suggest that the DHEA-induced cortisol response might indeed lead to enhanced attention but also to a decreased declarative memory performance. However, as stated earlier, other factors like increased fatigue or decreased motivation can not be excluded.

A recent animal study observed that DHEAS administration impaired selectively hippocampally mediated contextual fear conditioning (Fleshner et al., 1997). Since the authors observed similar effects after adrenalectomy (Pugh et al., 1997) they suggested that their findings might provide evidence for an antiglucocorticoid action of DHEA. However since it is known that low as well as high levels of GC can impair hippocampal plasticity (Diamond et al., 1992), the results of Fleshner et al. (1997) could also be explained by a DHEA induced increase in the corticosterone response to the stressful test paradigm. This interpretation might be supported by the fact that in the present study as well as in earlier experiments no declarative memory impairing effects of DHEA were observed under stress free conditions in humans (Wolf et al. 1997a,b; in press). Differences between the two species might be another possible reason for the discrepancy, especially since DHEA(S) concentrations are much lower in rodents than in humans (Fleshner et al., 1997; van Weerden et al., 1992).

In summary, DHEA treated elderly subjects who showed a trend towards a higher cortisol response to acute psychosocial stress recalled fewer items in a declarative memory task but performed better in an attention test after stress. A proposed antiglucocorticoid or anti-stress action of DHEA however should have protected declarative memory from the deterious effects of stress. Therefore the present study does not support the idea, that DHEA acts as functional antiglucocorticoid in the human hippocampus exposed to acute stress.

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