ORIGINAL ARTICLE

Relationships Among Plasma Dehydroepiandrosterone Sulfate and Cortisol Levels, Symptoms of Dissociation, and Objective Performance in Humans Exposed to Acute Stress

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Context: Recently, a growing body of research has provided evidence that dehydroepiandrosterone sulfate (DHEA-S) is involved in an organism's response to stress and that it may provide beneficial behavioral and neurotrophic effects.

Objective: To investigate plasma DHEA-S and cortisol levels, psychological symptoms of dissociation, and military performance.

Design: Prospective study.

Setting and Participants: Twenty-five healthy subjects enrolled in military survival school.

Results: The DHEA-S–cortisol ratios during stress were significantly higher in subjects who reported fewer symptoms of dissociation and exhibited superior military performance.

Conclusions: These data provide prospective, empirical evidence that the DHEA-S level is increased by acute stress in healthy humans and that the DHEA-S–cortisol ratio may index the degree to which an individual is buffered against the negative effects of stress.

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DEHYDROEPIANDROSTERONE (DHEA) is an endogenous hormone secreted by the adrenal cortex in response to adrenocorticotropin-releasing hormone (ACTH).[1] Dehydroepiandrosterone and its sulfated derivative, DHEA-S, were originally thought to be produced in situ in brain tissue and were referred to as neurosteroids.[2] At present, however, it is believed that the only source of brain DHEA-S is from the periphery.[3] A growing body of research has provided evidence that DHEA-S is involved in an organism's response to stress and that it may provide beneficial behavioral and neurotrophic effects.

In mice, DHEA-S release has been shown to be triggered by stress-induced release of ACTH and also exhibits memory-enhancing, antidepressant, anxiolytic, and antiaggression properties.[3-6] Neuronal and glial survival and differentiation have also been shown to be enhanced by DHEA-S in dissociated cultures of mouse embryo brain and intact rats.[7,8] Hippocampal neurotoxicity induced by corticosterone, oxidative stressors, and the glutamate agonist *N*-methyl-D-aspartate (NMDA) is prevented by DHEA-S.[7,8] In addition, DHEA-S prevents corticosterone-induced performance decrements.[9,10] Taken together, these findings suggest that DHEA-S may play a significant role in modulating vulnerability of the organism to negative consequences of stress.

In humans, levels of DHEA-S peak around ages 20 to 25 years and then decline to values of 20% to 30% at approximately 70 to 80 years of age.[11-14] Levels of DHEA-S are also reduced in a number of medical illnesses such as end-stage renal disease,[15] liver disease,[16] type 2 diabetes mellitus,[17] coronary artery disease,[18] and rheumatoid arthritis.[19] Levels of DHEA-S have also been noted to be reduced in individuals with chronic fatigue syndrome,[20] depression,[21-23] anxiety,[24] anorexia nervosa,[25] and schizophrenia.[26] In posttraumatic stress disorder (PTSD), levels of DHEA or DHEA-S have been variable. Levels have been noted to be increased in Israeli soldiers and Kosovo refugees with PTSD, but low in Kosovo refugees with PTSD who also had comorbid depression. Recently, increased release of DHEA was found in response to ACTH administration in women with PTSD but a negative relationship be-

tween the degree of ACTH-induced DHEA release and PTSD symptomatology (A.R., C.A.M., S.S., and D.C., unpublished data, 2004).

Consistent with preclinical data regarding the balance of DHEA-S to glucocorticoid levels, the DHEA-S–cortisol ratio in humans has been significantly associated with the degree of functional impairment[27-29] or the response to clinical intervention.[30] Taken together, these preclinical and clinical studies provide indirect evidence that the DHEA-S level and DHEA-S–cortisol ratio may play a role in modulating the impact of stress on a variety of processes in humans.

The present study was designed to evaluate levels of DHEA-S and cortisol, the DHEA-S–cortisol ratio, and the relationship of these hormone indexes with stress-induced symptoms of dissociation and objective performance in military personnel participating in survival school training. Previous investigations have demonstrated that survival school represents a valid, reliable model for the study of acute, uncontrollable stress in humans.[31-34] The results of these studies demonstrate that the stress experienced by subjects during survival school activates biological threat-response systems and elicits psychological symptoms of dissociation on a scale of magnitude comparable to the degree of arousal and dissociation noted in humans responding to real-world, threat-to-life experiences. Clinical studies have provided evidence that peritraumatic symptoms of dissociation represent a risk factor for the development of PTSD[35] and that such symptoms are positively associated with the stress-induced release of glucocorticoids.[33] On the basis of this and the preclinical and clinical literature suggesting that an increased DHEA-S–cortisol ratio may buffer against the negative impact of stress,[7,8,30] we hypothesized that individuals with a higher DHEA-S–cortisol ratio during stress exposure would be protected from the negative impact of survival school stress as evidenced by fewer symptoms of dissociation and superior military performance.

METHODS

Twenty-six consecutively recruited active duty military personnel were the subjects of this study. One female subject was removed from the data set, resulting in a study population of 25. As designated by their military operational specialty, 8 subjects were naval aviators, and 17 were nonaviating marines. The mean age was 25 years (SD, 4.4 years). Six subjects (24%) were married, and 19 (76%) were single. The average number of years in the service was 4.6 (SD, 4.1).

The methods used in this study have been reported in detail elsewhere.[31-34] In brief, before enrollment in this investigation, each participant completed in-processing into the survival training course. Recruitment of subjects was conducted by the principal investigator (C.A.M.). All subjects gave written, informed consent. As per survival training course requirements, all subjects provided documentation of physical examination and medical and psychiatric clearance before enrollment. All subjects were free of illicit substances as documented by results of urine toxicologic screening.

BASELINE ASSESSMENT

Five days before stress exposure, baseline saliva samples were obtained at 4 PM on the second day of didactic (classroom) activities. Immediately following the collection of salivary samples, baseline plasma samples were collected by one of the current investigators and Vladimir Coric, MD. Baseline salivary samples were again collected at 7:45 AM. Subjects then completed a modified self-report version of the Clinician-Administered Dissociative States Scale (CADSS) to rate their symptoms of dissociation during the classroom phase.[36]

The CADSS assesses the frequency and intensity of state symptoms of dissociation. The items of the instrument are designed to assess how perceptually in touch (or out of touch) an individual is vis-à-vis his or her environment during specific conditions (nonstressed and stressed). Although some of the items on the scale ask about one's sense of physical self (eg, "Do you feel as if you are looking at things outside of your body?" and "Do you feel as if you are watching the situation as an observer or spectator?"), other items ask about cognitive or perceptual distortions (eg, "Do colors seem to be diminished in intensity?"."Do sounds almost disappear or become much stronger than you would have expected?" "Do you space out or in some way lose track of what is going on?" and "Do you see things as if you were in a tunnel, or looking through a wide-angle photographic lens?"). The self-report scale contains 19 items, each of which is rated by subjects on a Likert scale of 0 (not at all) to 4 (extremely). A total score of 76 is possible.

STRESS SAMPLES

At the conclusion of the didactic phase of the training, soldiers participated in an experiential phase of survival training. During this phase, they were confined in a mock prisoner of war camp (POWC). In the POWC, each subject experienced various types of psychological stress. Broadly speaking, these included interrogations and problem-solving dilemmas designed to test the trainees' ability to use the information they learned during the didactic phase. As noted in previous publications,[31,33] these interrogations result in robust increases in cortisol and catecholamine levels, heart rate, and subjective distress and significant reductions in testosterone level. During the POWC stage, subjects also underwent uniform food and sleep deprivation. Before interrogation stress, all subjects had been deprived of food for approximately 8 hours and were physically inactive. During the 30-minute exposure to interrogation stress, subjects remained standing and relatively immobile; they did not engage in exercise or physical exertion. Immediately after interrogation, subjects were moved to a second room identical in appearance to the first, where their blood and saliva samples were collected by the research team (C.A.M. and G.H.) between 4:30 and 5 PM. Subjects provided the saliva samples before the venipuncture. After this, subjects continued to undergo uniform sleep and food deprivation until their release from the POWC. All participants were monitored by the survival school medical staff during the POWC stage and received water on a uniform schedule.

MILITARY PERFORMANCE

Survival school instructors performed an objective appraisal of observable military-relevant performance of each participant during the POWC phase of survival school. These performance assessment scores are part of the survival school program and are not available to the public. The overall rating score, however, is designed to reflect how well a participant in training is able to demonstrate specific behaviors and problem-solving abilities while experiencing acute stress. The performance ratings are scored on a scale that ranges from 0 (no skills demonstrated) to a maximum score of 4 (excellent demonstration of skills). Because these performance scores were generated independent of the research team and the measures col-

lected by the research team, they represent a double-blind opportunity to assess the relationship between operationally relevant military performance and the psychobiological measures that were of interest to the research team.[33]

RECOVERY SAMPLES

Twenty-four hours after the conclusion of POWC stress, recovery plasma and saliva samples were collected in all subjects. Because of programmatic constraints within the Navy survival school program, the collection of recovery samples occurred at 7:45 AM and not 4 PM as in our previous investigations of the Army survival school program. In addition to providing blood and saliva samples, subjects once again completed the CADSS. Subjects were asked to complete the CADSS using the stress they experienced during the interrogation phase of the POWC as their reference point.

Plasma samples were spun down in a refrigerated centrifuge, pipetted into microtubules, and frozen within 40 minutes of venipuncture. Samples were stored at −70°C from the time of initial collection until analyses were performed. Salivary samples were frozen and shipped with plasma samples to our laboratory within 24 hours of collection.

SALIVARY CORTISOL ANALYSIS METHODS

Saliva was collected in Salivette tubes (Sarstedt Inc, Newton, NC), centrifuged, and pipetted into two 1.5-mL plastic vials. The samples were shipped on dry ice to our laboratory and stored at −70°C until assayed. Salivary cortisol levels were analyzed by means of radioimmunoassay (IncStar Corp, Stillwater, Minn). The intra-assay and interassay coefficients of variation were 4.2% and 6.1%, respectively.

PLASMA DHEA-S ANALYSIS METHODS

Frozen plasma samples were used and processed in batch by means of DHEA-S commercial radioimmunoassay kits (Diagnostic Systems Laboratories, Inc, Webster, Tex). Determinations were performed on duplicate 10-mL plasma samples according to the manufacturer's recommendations, using supplied rabbit polyclonal anti-DHEA-S antibody–coated tubes. Plasma DHEA-S concentrations were measured with a sensitivity (detectability) of approximately 2 μg/dL and intra-assay and interassay coefficients of variation of 9% and 15%, respectively.

DATA ANALYSIS

Separate repeated-measures analyses of variance (ANOVAs) using the time factors baseline-stress and baseline-recovery were performed to detect whether exposure to stress significantly affected levels of plasma DHEA-S and plasma and salivary cortisol. To control for diurnal variation, the cortisol samples collected at the 4 PM point at baseline were compared with the cortisol samples collected at the stress time point. Similarly, the ANOVAs examining whether salivary cortisol levels had returned to the reference range after the conclusion of the training used the 7:45 AM salivary cortisol samples, because these were closely associated with the time of saliva assessment on the day of recovery (7:45 AM).

Pearson correlation analyses were used to evaluate the relationships among the assessed hormone levels (DHEA-S and cortisol) and the relationships among the hormones and the independent variables of age and weight.

Spearman rank correlation analyses were used to compare the DHEA-S–salivary cortisol ratios from the baseline, stress, and recovery time points with psychological symptoms of dissociation (CADSS total scores) and military performance scores. Exploratory post hoc analyses were planned for individual CADSS items in the event that a significant relationship was observed between DHEA-S–cortisol ratios and CADSS total score.

Finally, separate stepwise linear regression analyses were used to examine whether or how well the independent variables of age, rank, time in service, or the DHEA-S–salivary cortisol ratio would explain the variance in stress-induced symptoms of dissociation (the CADSS total score) and in objectively assessed military performance.

RESULTS

The variables of age, rank, and time in the service did not contribute to variance in the hormone or the psychological data, and thus were removed from the analyses.

PSYCHOLOGICAL MEASURES

The mean CADSS score at baseline was 1.0 (SD, 1.6), whereas the poststress CADSS score was 17.4 (SD, 13.0). This increase was statistically significant ($F_{1,24}=40.8$ [$P<.001$]). In the published literature this would be considered a moderate level of dissociation.[37]

MILITARY PERFORMANCE SCORES

The mean, objectively assessed military performance rating for subjects was 2.3 (SD, 0.7), with a range of 1.0 to 3.8.

HORMONE VALUES

Compared with baseline, there was a significant increase in DHEA-S level in response to stress (baseline, 27.81 μg/dL [SD, 11.06 μg/dL] [SI units {calculated with a conversion factor of 0.02714}, 0.755 μmol/L {SD, 0.30 μmol/L}]; stress, 60.12 μg/dL [SD, 26.15 μg/dL] [1.63 μmol/L {SD, 0.71 μmol/L}]; $F_{1,21}=76.1$ [$P<.001$]), and it remained significantly increased compared with baseline at the recovery time point (27.81 μg/dL [SD, 11.06 μg/dL] [0.755 μmol/L {SD, 0.30 μmol/L}] vs 37.32 μg/dL [SD, 16.98 μg/dL] [1.01 μmol/L {SD, 0.46 μmol/L}]; $F_{1,18}=22.4$ [$P<.001$]). The DHEA-S values at recovery were significantly reduced compared with the stress time point ($F_{1,17}=68.2$ [$P<.001$]). Plasma cortisol level was also significantly increased by exposure to survival school stress and remained significantly elevated compared with baseline at the recovery time point (baseline, 8.6 μg/dL [237.3 nmol/L] [SD, 3.8 μg/dL {104.8 nmol/L}]; stress, 31.1 μg/dL [858.0 nmol/L] [SD, 5.8 μg/dL {160.0 nmol/L}]; recovery, 19.9 μg/dL [549.0 nmol/L] [SD, 7.0 μg/dL {193.1 nmol/L}]) ($F_{1,22}=168.2$ [$P<.001$] and $F_{1,23}=55.8$ [$P<.001$], baseline vs stress and baseline vs recovery, respectively). Similarly, compared with baseline levels, salivary cortisol level was significantly increased by exposure to survival school stress (baseline, 0.14 μg/dL [3.9 nmol/L] [SD, 0.04 μg/dL {1.1 nmol/L}]; stress, 0.87 μg/dL [24.0 nmol/L] [SD, 0.45 μg/dL {12.4 nmol/L}]) ($F_{1,24}=62.5$ [$P<.001$]). However, compared with baseline morning values, morning salivary cortisol levels collected at recovery (recovery value, 0.49 μg/dL [13.5 nmol/L] [SD,

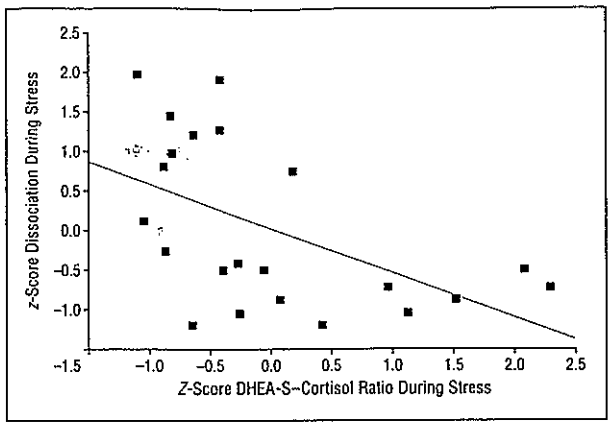

Figure 1. Correlation between dehydroepiandrosterone sulfate (DHEA-S)–cortisol ratio and stress-induced symptoms of dissociation in 22 healthy subjects enrolled in military survival school (R^2=0.29; Spearman ρ=−0.63 [P=.002]).

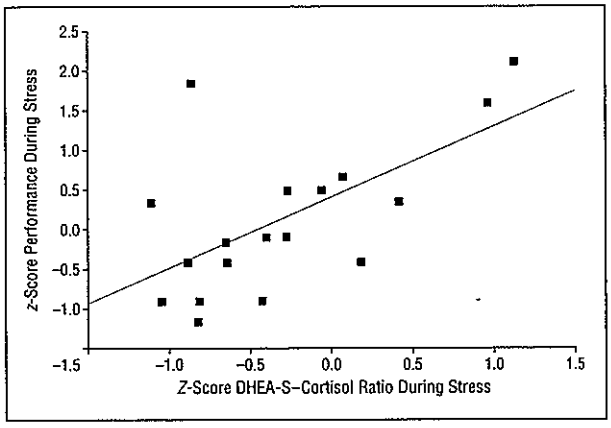

Figure 2. Correlation between dehydroepiandrosterone sulfate (DHEA-S)–cortisol ratio during stress and military performance in 18 healthy subjects enrolled in military survival school (R^2=0.37; Spearman ρ=5.2 [P=.03]).

0.20 µg/dL [5.5 nmol/L]]) tended to be significantly higher only at the recovery time point ($F_{1,24}$=3.7 [P=.06]).

CORRELATION ANALYSES

No significant correlations were observed between plasma levels of DHEA-S and cortisol or between plasma levels of DHEA-S and salivary levels of cortisol at any of the assessment time points (baseline and stress or recovery). Similarly, Spearman rank correlation analyses did not reveal a significant correlation between plasma cortisol level and poststress CADSS scores (r=0.16; P=.41). However, there was a significant positive relationship between salivary cortisol level during stress exposure and the poststress CADSS scores (r=0.4; P<.05) and a trend for a significant negative relationship between stress-induced levels of DHEA-S and poststress CADSS scores (r=−0.4; P=.08). Finally, as shown in **Figure 1**, there was a significant negative correlation between the DHEA-S–salivary cortisol ratio during stress and the poststress CADSS scores (r=−0.63; P=.002).

Analysis of individual CADSS items indicated that there were significant negative relationships between the DHEA-S–salivary cortisol ratio during stress and CADSS items 2 (feeling unreal as if in a dream; r=−0.44; [P<.04]), 6 (feeling disconnected from one's body; r=−0.54 [P=.009]), 10 (colors appearing to be diminished in intensity; r=−0.6 [P=.004]), 11 (feeling as if one is viewing the world in a tunnel or looking through a wide-angle lens; r=−0.6 [P=.003]), 15 (feelings of being spaced out or of losing track of what is going on; r=−0.44 [P=.04]), 16 (sounds disappearing or becoming much stronger than expected; r=−0.51 [P=.01]), 17 (things having a special sense of clarity; r=−0.49 [P=.02]), and 18 (feeling as if one is looking at world as if in a fog, people appearing far away or unclear; r=−0.72 [P<.001]).

With regard to the relationship between objective military performance and the indexes of DHEA-S and cortisol levels and dissociation, as shown in **Figure 2**, there was a significant positive correlation between the DHEA-S–salivary cortisol ratio during stress and the military performance scores (r=0.61 [P=.008]) and a significant negative correlation between stress-induced levels of salivary cortisol and military performance (r=−0.51 [P<.01]). In addition, and similar to the findings of our previous investigations, there was a significant negative relationship between stress-induced symptoms of dissociation (CADSS scores) and military performance (r=−0.51 [P<.01]).

No significant relationships were observed between baseline hormone values, recovery hormone values, DHEA-S–cortisol ratios at baseline or at recovery, and the outcome measures of dissociative symptoms and military performance scores in response to stress.

REGRESSION ANALYSES

Stepwise linear regression analysis using poststress CADSS dissociation scores as the dependent variable and the DHEA-S–salivary cortisol ratio and plasma levels of DHEA-S and cortisol during stress as the independent variables showed that the model was significant ($F_{1,19}$=7 [P=.02]). The adjusted multivariate coefficient of determination (R^2) for the model was 0.24 for the predictor DHEA-S–salivary cortisol ratio during stress. The model did not improve when the variables plasma levels of DHEA-S and cortisol during stress were added. The standardized β coefficient value for DHEA-S–salivary cortisol ratio during stress was −0.53, with a t value of −2.6 (P=.02).

Stepwise linear regression analysis using military performance scores as the dependent variable and the DHEA-S–salivary cortisol ratio and plasma levels of DHEA-S and cortisol during stress as the independent variables showed that the model was significant ($F_{1,16}$=5.6 [P=.03]). The adjusted multivariate coefficient of determination (R^2) for the model was 0.23 for the predictor DHEA-S–salivary cortisol ratio during stress. The model did not improve when the variable plasma level of DHEA-S or cortisol during stress was added. The standardized β coefficient value for DHEA-S–salivary cortisol ratio during stress was 0.52, with a t value of 2.4 (P=.03).

COMMENT

The principal finding of this study is that individuals with a higher DHEA-S–salivary cortisol ratio during stress ex-

perienced fewer symptoms of dissociation and exhibited superior military performance. Because indexes of dissociation and military performance presumably index central processes, the data herein provide support that in healthy humans, the ratio or balance between circulating levels of DHEA-S to unbound cortisol may help buffer against centrally mediated, negative effects of stress.

One implication of the present findings is that a low DHEA-S–cortisol ratio may be associated with vulnerability to stress-induced symptoms of dissociation. In the future it may be fruitful to conduct clinical trials designed to prospectively evaluate whether augmentation of DHEA-S levels in humans, before the time of their exposure to stress, will confer a protective effect, as evidenced by diminished peritraumatic dissociation and improved cognitive performance.

Military performance was significantly and positively associated with DHEA-S–cortisol ratios. Because the rating scales used by the military have not been made available to the public, the degree to which these scales relate to more traditional cognitive or psychological measures has not yet been fully established. However, in 3 separate investigations, psychological symptoms of dissociation—as measured by the CADSS—have been shown to be associated with poor military performance. Because the military performance scores reflect the capacity of soldiers' cognitive and decision-making abilities during stress, the present finding of a positive relationship between military performance scores and the DHEA-S–cortisol ratio adds weight to the idea that increased levels of DHEA-S are associated with an antistress effect on human cognition. These findings are consistent with those of previous clinical studies linking superior cognitive performance with higher concentrations of DHEA.[38]

Although no preclinical studies deal specifically with symptoms of dissociation, much is known about the relationship between levels of cortisol, DHEA-S, and glutamate and stress-induced neurotoxicity. However, it is not known at present whether stress-induced dissociation in humans is related to stress-induced neurotoxicity, as reported in the preclinical literature.

A host of preclinical investigations have shown that glucocorticoids can be neurotoxic and that DHEA-S exerts a potent antiglucocorticoid effect peripherally and centrally.[7] For example, prolonged exposure to high levels of circulating corticosterone in rats increases the age-related rate at which hippocampal pyramidal neurons are lost.[39] Glucocorticoids have also been shown to potentiate neurodegeneration induced by anoxia and glutamate analogues. The neurotoxic effects of glucocorticoids can be attenuated or blocked by in vivo and in vitro administration of DHEA-S.[7,8]

Preclinical investigations suggest several possible mechanisms by which DHEA-S or DHEA may protect against dissociation or improve cognition in humans. For example, antiglucocorticoid effects of DHEA have been demonstrated in many tissues, including brain.[40-45] Within the brain, region-specific metabolism of DHEA may ultimately control the nature of DHEA effects on cognition and behavior.[46] For instance, 7α-hydroxylated metabolites of DHEA have been shown to interfere with the nuclear uptake of activated glucocorticoid receptors in the neurons of the hippocampus.[46] Dehydroepiandrosterone also protects against excitatory amino acid– and oxidative stress–induced damage, restores cortisol-induced decrements in long-term potentiation, regulates programmed cell death, and promotes neurogenesis in the hippocampus.[7,8,47-50] Thus it is possible that the military personnel exhibiting higher DHEA-S–cortisol ratios during extreme stress in this study came to survival training with brain structures and functional capacities that protected them from dissociation during the interrogation stress.

Preclinical and clinical data suggest that the reduced levels of dissociation in subjects with an increased DHEA-S–salivary cortisol ratio during stress may be due, in part, to the action of DHEA-S at NMDA receptors and/or at the γ-aminobutyric acid–benzodiazepine receptor complex, perhaps at the level of the hippocampus or frontal cortex. Dehydroepiandrosterone sulfate serves as a negative modulator of the γ-aminobutyric acid–benzodiazepine receptor complex,[40,51,52] and there is evidence of altered benzodiazepine receptor modulation and sensitivity in stress-related disorders characterized by symptoms of dissociation, such as PTSD.[53] Furthermore, DHEA-S also positively modulates NMDA receptors, which have been implicated in dissociative phenomena in humans as assessed by the CADSS.[37] Thus, it is reasonable to speculate that the reduced levels of dissociation in subjects with a high DHEA-S–cortisol ratio may be due, in part, to the effect of DHEA on NMDA receptors and/or the effect of DHEA at the γ-aminobutyric acid–benzodiazepine receptor complex, perhaps at the level of the hippocampus.

There are several limitations to this study. First, all subjects in survival school training experienced food deprivation before stress exposure. Because dieting in clinically obese individuals has been reported to result in an increase in DHEA-S level,[54] it is theoretically possible that the increase in DHEA-S levels noted in the present subjects may have been, in part, influenced by this factor. However, because food deprivation was kept uniform across subjects, this factor cannot account for the significant relationships between the DHEA-S–cortisol ratios and the symptoms of dissociation and military performance.

All subjects also experienced sleep deprivation, raising the possibility that alterations in the diurnal variation in DHEA-S and cortisol levels may have contributed to the findings of this study. Although possible, this is unlikely to explain the present findings for 2 reasons. First, the findings of previous studies in military subjects exposed to high stress have shown that the diurnal variation of hormones is extremely small relative to the very large alterations of these hormones induced by exposure to acute stress.[31] Second, sleep deprivation was kept uniform across all subjects.

Another limitation is the relatively small number of subjects in this study. It is possible that the large amount of the variance explained in the regression analyses may be due to the relative homogeneity of these military personnel, and the present data may not generalize to the general population. However, the data may be relevant for civilian groups (eg, firefighters, police officers, and

emergency personnel) who are at increased risk for stress exposure and stress-related illness.

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REFERENCES

1. Nieschlag E, Loriaux DL, Ruder HJ, Zucker IR, Kirschner MA, Lipsett MB. The secretion of dehydroepiandrosterone and dehydroepiandrosterone sulphate in man. *J Endocrinol.* 1973;57:123-134.
2. Majewska MD, Demirgoren S, Spivak CE, London ED. The neurosteroid dehydroepiandrosterone sulfate is an allosteric antagonist of the GABAA receptor. *Brain Res.* 1990;526:143-146.
3. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. *Front Neuroendocrinol.* 2000;21:1-56.
4. Melchior CL, Ritzmann RF. Dehydroepiandrosterone is an anxiolytic in mice on the plus maze. *Pharmacol Biochem Behav.* 1994;47:437-441.
5. Robel P, Baulieu EE. Dehydroepiandrosterone (DHEA) is a neuroactive neurosteroid. *Ann N Y Acad Sci.* 1995;774:82-110.
6. Roberts E. Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) as neural facilitators: effects on brain tissue in culture and on memory in young and old mice: a cyclic GMP hypothesis of action of DHEA and DHEAS in nervous system and other tissues. In: Kalimi M, Regelson W, eds. *The Biologic Role of Dehydroepiandrosterone (DHEA).* Berlin, Germany: W de Gruyter; 1990:13-42.
7. Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid–induced neurotoxicity. *Proc Natl Acad Sci U S A.* 1998;95:1852-1857.
8. Kimonides VG, Spillantini MG, Sofroniew MV, Fawcett JW, Herbert J. Dehydroepiandrosterone antagonizes the neurotoxic effects of corticosterone and translocation of stress-activated protein kinase 3 in hippocampal primary cultures. *Neuroscience.* 1999;89:429-436.
9. Fleshner M, Pugh CR, Tremblay D, Rudy JW. DHEA-S selectively impairs contextual-fear conditioning: support for the antiglucocorticoid hypothesis. *Behav Neurosci.* 1997;111:512-517.
10. Frye CA, Lacey EH. The neurosteroids DHEA and DHEAS may influence cognitive performance by altering affective state. *Physiol Behav.* 1999;66:85-92.
11. Labrie F, Belanger A, Cusan L, Gomez J-L, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab.* 1997;82:2396-2402.
12. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab.* 1984;59:551-555.
13. Orentreich N, Brind JL, Bogelman JH, Andres R, Baldwin H. Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. *J Clin Endocrinol Metab.* 1992;75:1002-1004.
14. Sulcova J, Hill M, Starka L. Age and sex related differences in serum levels of unconjugated dehydroepiandrosterone and its sulphate in normal subjects. *J Endocrinol.* 1997;154:57-62.
15. Zumoff B, Walter L, Rosenfeld RS, Strain JJ, Degen K, Strain GW, Levin J, Fukushima D. Subnormal plasma adrenal androgen levels in men with uremia. *J Clin Endocrinol Metab.* 1980;51:801-805.
16. Floreani A, Titta M, Plebani M, Faggian D, Chiaramonte M, Naccarato R. Sex hormone changes in post-menopausal women with primary biliary cirrhosis (PBC) and with cryptogenic chronic liver disease. *Clin Exp Obstet Gynecol.* 1991;18:229-234.
17. Yamauchi A, Takei I, Kasuga A, Kitamura Y, Ohashi N, Nakano S, Takayama S, Nakamoto S, Katsukawa F, Saruta T. Depression of dehydroepiandrosterone in Japanese diabetic men: comparison between non–insulin dependent diabetes mellitus and impaired glucose tolerance. *Eur J Endocrinol.* 1996;135:101-104.
18. Herrington DM, Gordon GB, Achuff SC, Trejo JF, Weisman HJ, Kwitervich PO, Pearson TA. Plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate in patients undergoing diagnostic coronary angiography. *J Am Coll Cardiol.* 1990;16:862-870.
19. Masi AT. Sex hormones and rheumatoid arthritis: cause or effect relationships in a complex pathophysiology? *Clin Exp Rheumatol.* 1995;13:227-240.
20. Scott LV, Salahuddin F, Cooney J, Svec F, Dinan TG. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. *J Affect Disord.* 1999;54:129-137.
21. Goodyer IM, Herbert J, Altham PME, Pearson J, Secher SM, Shiers HM. Adrenal secretion during major depression in 8-16 year olds, I: altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. *Psychol Med.* 1996;26:245-256.
22. Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, Ormiston S, Johnson R, Canick J, Brizendine L, Weingartner H. Dehydroepiandrosterone (DHEA) treatment of depression. *Biol Psychiatry.* 1997;41:311-318.
23. Micheal A, Jenaway A, Paykel ES, Herbert J. Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biol Psychiatry.* 2000;48:989-995.
24. Fava M, Rosenbaum JF, MacLaughlin RA, Tesar GE, Pollack MH, Cohen LS, Hirsch M. Dehydroepiandrosterone-sulfate/cortisol ratio in panic disorder. *Psychiatry Res.* 1989;28:345-350.
25. Zumoff B, Walsh BT, Katz JL, Levin J, Rosenfeld RS, Kream J, Weiner H. Subnormal plasma dehydroepiandrosterone to cortisol ratio in anorexia nervosa: a second hormonal parameter of ontogenic regression. *J Clin Endocrinol Metab.* 1983;56:668-672.
26. Oades RD, Schepker R. Serum gonadal steroid hormones in young schizophrenic patients. *Psychoneuroendocrinology.* 1994;19:373-385.
27. Soendergaard HP, Hansson LO, Theorell T. Elevated blood levels of dehydroepiandrosterone sulphate vary with symptom load in posttraumatic stress disorder: findings from a longitudinal study of refugees in Sweden. *Psychother Psychosom.* 2002;71:298-303.
28. Goodyer IM, Herbert J, Altham PME. Adrenal steroid secretion and major depression in 8-16 year olds, III: influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. *Psychol Med.* 1998;28:253-255.
29. Soendergaard HP, Theorell T. A longitudinal study of hormonal reactions accompanying life events in recently resettled refugees. *Psychother Psychosom.* 2003;72:49-58.
30. Cruess DG, Antoni MH, Kumar M, Ironson G, McCabe P, Fernandez JB, Fletcher MA, Schneiderman N. Cognitive-behavioral stress management buffers decreases in dehydroepiandrosterone sulfate (DHEA-S) and increases in the cortisol/DHEA-S ratio and reduces mood disturbance and perceived stress among HIV-seropositive men. *Psychoneuroendocrinology.* 1999;24:537-549.
31. Morgan CA III, Wang S, Mason J, Hazlett G, Fox P, Southwick SM, Charney DS, Greenfield G. Hormone profiles in humans experiencing military survival training. *Biol Psychiatry.* 2000;47:891-901.
32. Morgan CA III, Wang S, Southwick SM, Rasmusson A, Hauger R, Charney DS. Plasma neuropeptide-Y in humans exposed to military survival training. *Biol Psychiatry.* 2000;47:902-909.
33. Morgan CA III, Wang S, Hazlett G, Rassmusson A, Anderson G, Charney DS. Relationships among cortisol, catecholamines, neuropeptide Y and human performance during uncontrollable stress. *Psychosom Med.* 2001;63:412-442.
34. Morgan CA III, Hazlett G, Wang S, Richardson G, Schnurr P, Southwick SM. Symptoms of dissociation in humans experiencing acute uncontrollable stress: a prospective investigation. *Am J Psychiatry.* 2001;158:1239-1247.
35. Marmar CR, Weiss DS, Metzler TJ, Delucchi KL, Best SR, Wentworth KA. Longitudinal course and predictors of continuing distress following critical incident exposure in emergency services personnel. *J Nerv Ment Dis.* 1999;187:15-22.
36. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress.* 1998;11:125-136.
37. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methly-D-aspartate receptor antagonists. *Arch Gen Psychiatry.* 2000;57:270-276.

38. Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C. Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. *Psychoneuroendocrinology*. 1998; 23:617-629.
39. Hortnagl H, Berger ML, Havelec L, Hornykeiwicz O. Role of glucocorticoids in the cholinergic degeneration in rat hippocampus induced by ethylcholine aziridinium (AF64A). *J Neurosci*. 1993;13:2939-2945.
40. Demirgoren S, Majewska MD, Spivak CE, London ED. Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the GABA A receptor. *Neuroscience*. 1991;45:127-135.
41. Kishimoto Y, Hoshi M. Dehydroepiandrosterone sulphate in rat brain: incorporation from blood and metabolism in vivo. *J Neurochem*. 1972;19:2207-2215.
42. Blauer KL, Poth M, Rogers W, Bernton E. DHEA antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. *Endocrinology*. 1991;129: 3174-3179.
43. Browne ES, Wright BE, Porter JR, Svec F. Dehydroepiandrosterone: antiglucocorticoid action in mice. *Am J Med Sci*. 1992;303:366-371.
44. Daynes RA, Dudley DJ, Araneo BA. Regulation of murine lymphokine production in vivo, II: dehydroepiandrosterone is a natural enhancer of interleukin 2 synthesis by helper T cells. *Eur J Immunol*. 1990;20:793-802.
45. Morfin R, Starka L. Neurosteroid 7-hydroxylation products in the brain. *Int Rev Neurobiol*. 2001;46:79-95.
46. Rose KA, Stapleton G, Dott K, Kieny MP, Best R, Schwarz M, Russell DW, Bjorkheim I, Seckl J, Lathe R. Cyp7b, a novel brain cytochrome P450, catalyzes the synthesis of neurosteroids 7α-hydroxy dehydroepiandrosterone and 7α-hydroxy pregnenolone. *Proc Natl Acad Sci U S A*. 1997;94:4925-4930.
47. Bastianetto S, Ramassamy C, Poirier J, Quirion R. Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage. *Mol Brain Res*. 1999;66:35-41.
48. Kaminska M, Harris J, Gilsbers K, Dubrovsky B. Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP: implications for depression. *Brain Res Bull*. 2000;52:229-234.
49. Karishma KK, Herbert J. Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression. *Eur J Neurosci*. 2002;16:445-453.
50. Zhang L, Li B, Ma W, Barker JL, Chang YH, Zhao W, Rubinow DR. Dehydroepiandrosterone (DHEA) and its sulfated derivative (DHEAS) regulate apoptosis during neurogenesis by triggering the Akt signaling pathway in opposing ways. *Brain Res Mol Brain Res*. 2002;98:58-66.
51. Majewska MD, Schwartz RD. Pregnenolone-sulfate: an endogenous antagonist of the γ-aminobutyric acid receptor complex in brain? *Brain Res*. 1987;404:355-360.
52. Majewska MD, Mienville J-M, Vicini S. Neurosteroid pregnenolone sulfate antagonizes electrophysiological responses to GABA in neurons. *Neurosci Lett*. 1988; 90:279-284.
53. Gavish M, Laor N, Bidder M, Fisher D, Fonia O, Muller U, Reiss A, Wolmer L, Karp L, Weizman R. Altered platelet peripheral type benzodiazepine receptor in posttraumatic stress disorder. *Neuropsychopharmacology*. 1996;14:181-186.
54. Jakubowicz DJ, Beer NA, Beer RM, Nestler JE. Disparate effects of weight reduction by diet on serum dehydroepiandrosterone-sulfate levels in obese men and women. *J Clin Endocrinol Metab*. 1995;80:3373-3376.