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Sex Differences in Endocrine and Psychological Responses to Psychosocial Stress in Healthy Elderly Subjects and the Impact of a 2-Week Dehydroepiandrosterone Treatment*

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ABSTRACT

Evidence from animal as well as human studies has suggested that significant sex differences exist in hypothalamus-pituitary-adrenal axis (HPA) activity. As gonadal steroids could be important modulators of HPA sex differences, stress responses were investigated in subjects of advanced age after dehydroepiandrosterone (DHEA) or placebo treatment.

After a 2-week treatment with 50 mg DHEA daily or placebo, 75 men and women (mean age, 67.6 yr) were exposed to the Trier Social Stress Test (TSST). The TSST is a brief psychosocial stress that consists of a free speech and mental arithmetic task in front of an audience. The results show that the TSST induced significant increases in ACTH, salivary free cortisol, total plasma cortisol, norepinephrine, and heart rates (all $P < 0.0001$) as well as decreased positive affect in the elderly ($P = 0.0009$). Men showed larger stress responses in ACTH ($P = 0.004$), salivary free cortisol ($P = 0.044$), and plasma total cortisol ($P = 0.076$) compared to women. No sex differences were observed in norepinephrine, epinephrine, or heart rate responses. In contrast to ACTH and cortisol response differences, women reported that they were significantly more stressed by the TSST than men ($P = 0.0051$).

Women treated with DHEA showed ACTH stress responses similar to those of men, but significantly enhanced compared to those of women taking placebos ($P < 0.009$). No other stress response differences emerged between DHEA and placebo groups. Finally, DHEA treatment did not result in an improvement of subjective well-being.

We conclude that elderly men show larger HPA responses than women to psychosocial stress, as studied in the TSST. Estrogen effects on hypothalamic CRF-producing neurons might be responsible for these sex differences. (*J Clin Endocrinol Metab* **83:** 1756–1761, 1998)

SIGNIFICANT sex differences exist in hypothalamus-pituitary-adrenal (HPA) axis responsiveness in rodents as well as in humans. Although in rats, there appears to be a clear hyperresponsiveness in basal as well as stress-related HPA activity in females (1, 2), findings are more controversial in humans. On the level of the adrenals, some evidence supports the idea that women have a greater sensitivity to ACTH than men (3). Additionally, women show greater and more prolonged endocrine reactions to ovine CRF (4) or to the combined dexamethasone-CRF test (5). After administration of the centrally active cholinesterase inhibitor physostigmine, only a trend toward higher endocrine reactions in women compared to men was reported (6). A contrasting picture has emerged concerning psychosocial stress responses. In several independent studies, young male subjects consistently showed significantly higher HPA responses than female participants (7–9).

Early studies by Kitay (1, 2) have shown that sex steroids, especially estradiol, exert a potentiating effect on the HPA axis in animals. A similar influence of estradiol in healthy young men was recently reported by this laboratory (10), supporting the view of a substantial influence of sex steroids on HPA activity. As aging is characterized by significantly decreasing gonadal steroid levels, investigations of potential sex differences in HPA responses to psychosocial stress in the elderly are warranted.

The present report describes the responsiveness of the HPA axis and the sympathetic nervous system to the Trier Social Stress Test (TSST), a potent psychosocial stress protocol in healthy elderly men and women. In addition, the effects of a 2-week treatment with the sex hormone precursor dehydroepiandrosterone (DHEA) on HPA responses were studied.

Subjects and Methods

Subjects

Thirty-nine healthy male (67.4 ± 0.9 yr) and 36 healthy postmenopausal female (67.6 ± 0.8 yr) participants underwent a comprehensive medical examination for past or current health problems. Subjects with

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psychiatric, endocrine, cardiovascular, other chronic diseases or those medicated with psychoactive drugs, β-blockers, estrogens, or glucocorticoids were excluded from participation. Ten smokers, who reported smoking less than 15 cigarettes/day, were included. In each experimental condition there were 2 or 3 smokers, respectively. The mean body mass index was 25.8 ± 0.4 (± SEM) for men and 25.5 ± 0.6 (± SEM) for women. The study protocol was approved by the ethics committee of the University of Trier.

Hormonal treatment

The present experimental study applied a placebo-controlled, double blind design. For 2 weeks, 40 subjects took 50 mg DHEA daily (Prasteron, Audor Pharma, Regensburg, Germany), whereas 35 sex-, age-, and body mass index-matched controls received placebo (see Table 1). One DHEA capsule contained 50 mg DHEA and lactose; placebo capsules contained lactose only. Subjects were instructed to take the capsules at bedtime each day.

Experimental protocol

Each subject reported twice to the laboratory. The first appointment, between 0800–0930 h, included a medical examination, distribution of capsules, and completion of a mood questionnaire (see below). Two weeks later, subjects were exposed to the psychological stressor at the second appointment, between 0900–1330 h. After catheter insertion and a rest period of 45 min, a mood questionnaire (see below) was completed, and subjects were interviewed about any symptoms experienced in response to the DHEA/placebo treatment. After the resting period, the first blood and saliva samples were collected. Thereafter, subjects were confronted with the TSST (11), which consists of a free speech and mental arithmetic task of 13-min duration performed in front of an audience. Additional blood and saliva samples were obtained 1, 10, 20, 30, 45, 60, 90, and 120 min after stress exposure. Mood and perceived stressfulness were assessed by visual analog scales (VAS; see below) after stress exposure.

Assessment of well-being, mood, and perceived stress

The German self-rating depression scale was employed to measure the extent of depression (12). Three subjects (self-rating depression scale scores >48) were excluded from all statistical analyses, because of a possible impact of depression on HPA responses (13).

Nine items were used to investigate possible changes in physical or psychological conditions after the 2-week treatment, including stress resilience, well-being, quality of sleep, stressfulness of daily activities, quality of sex, relaxation, pain, general activity, and level of concentration. At the first appointment, momentary mood was assessed with a German mood questionnaire (14). This questionnaire measures elevated *vs.* depressed mood, wakefulness *vs.* sleepiness, and calmness *vs.* restlessness. At the second appointment, momentary mood was assessed before and after the stress task. Nine VASs were employed for participants' ratings of the stressfulness of the TSST.

Blood and saliva sampling

At both laboratory appointments, basal blood samples were obtained for measurement of basal gonadal steroids. During the second appointment, one blood sample and one saliva sample were collected directly before starting the stress exposure. The remaining eight samples were collected 1, 10, 20, 30, 45, 60, 90, and 120 min after cessation of stress. Saliva was collected by the subjects, using Salivette (Sarstedt, Rommelsdorf, Germany) collection devices.

Biochemical analyses

Two basal blood samples (before and after treatment) were used to measure DHEA sulfate (DHEA-S; by enzyme-linked immunosorbent assay, IBL, Hamburg, Germany), androstendione plasma levels (by RIA, IBL), estradiol and free testosterone levels (by RIAs, Biermann, Bad Nauheim, Germany), and total testosterone levels (by RIA, IBL). The free cortisol concentration in saliva was measured using a time-resolved immunoassay with fluorometric detection as described in detail previously (15). The total plasma cortisol was measured with a RIA (IBL). ACTH was determined with a two-site chemiluminescence assay (Ni-

TABLE 1. Sex, age, body mass index (BMI), and endocrine parameters before and after a 2-week treatment with DHEA or placebo

	Placebo			DHEA			*P*
	Women	Men	Total group	Women	Men	Total group	
No.	18	17	35	18	22	40	NS
Age (yr)	68.4 ± 1.1	66.6 ± 1.4	67.5 ± 0.9	67.1 ± 1.1	68.0 ± 1.2	67.6 ± 0.8	NS
BMI	26.1 ± 1.0	26.4 ± 0.6	26.2 ± 0.6	24.9 ± 0.8	25.3 ± 0.6	25.1 ± 0.5	NS
DHEA-S before treatment (μg/L)	0.70 ± 0.1	1.12 ± 0.1	0.92 ± 0.1	0.65 ± 0.7	0.94 ± 0.1	0.81 ± 0.1	0.0001[a,b] 0.043[c]
DHEA-S after treatment (μg/mL)	0.71 ± 0.1	1.1 ± 0.1	0.89 ± 0.1	3.50 ± 0.3	3.15 ± 0.2	3.31 ± 0.2	
A'dione before treatment (ng/mL)	0.98 ± 0.1	1.47 ± 0.2	1.21 ± 0.1	0.93 ± 0.9	1.38 ± 0.1	1.17 ± 0.1	0.0001[a,b] 0.0003[c]
A'dione after treatment (ng/mL)	1.03 ± 0.1	1.30 ± 0.2	1.16 ± 0.1	1.9 ± 0.18	1.74 ± 0.1	1.79 ± 0.1	0.03[d]
Estradiol before treatment (pg/mL)	18.1 ± 2.9	26.9 ± 1.8	22.3 ± 1.9	20.1 ± 4.8	25.9 ± 1.3	23.3 ± 2.8	0.0001[d] 0.041[b]
Estradiol after treatment (pg/mL)	14.1 ± 0.8	27.8 ± 1.4	20.8 ± 1.5	23.8 ± 1.7	29.7 ± 1.4	27.1 ± 1.2	
Free Testo before treatment (pg/mL)	2.44 ± 0.2	32.3 ± 3.7	16.5 ± 3.1	3.19 ± 0.7	28.0 ± 2.1	16.8 ± 2.3	0.013[a] 0.0001[d]
Free Testo after treatment (pg/mL)	2.58 ± 0.2	35.0 ± 3.1	17.9 ± 3.2	4.85 ± 0.6	28.9 ± 2.0	18.1 ± 2.2	
Total Testo before treatment (ng/mL)	0.23 ± 0.02	4.04 ± 0.42	2.03 ± 0.38	0.26 ± 0.06	3.59 ± 0.30	2.05 ± 0.31	0.0001[d] 0.0037[b]
Total Testo after treatment (ng/mL)	0.24 ± 0.02	3.77 ± 0.26	1.90 ± 0.33	0.54 ± 0.07	4.10 ± 0.20	2.50 ± 0.32	

A'dione, Androstenedione; Testo, Testosterone.
[a] Time effect.
[b] Group by time effect.
[c] Sex by time effect.
[d] Sex effect.

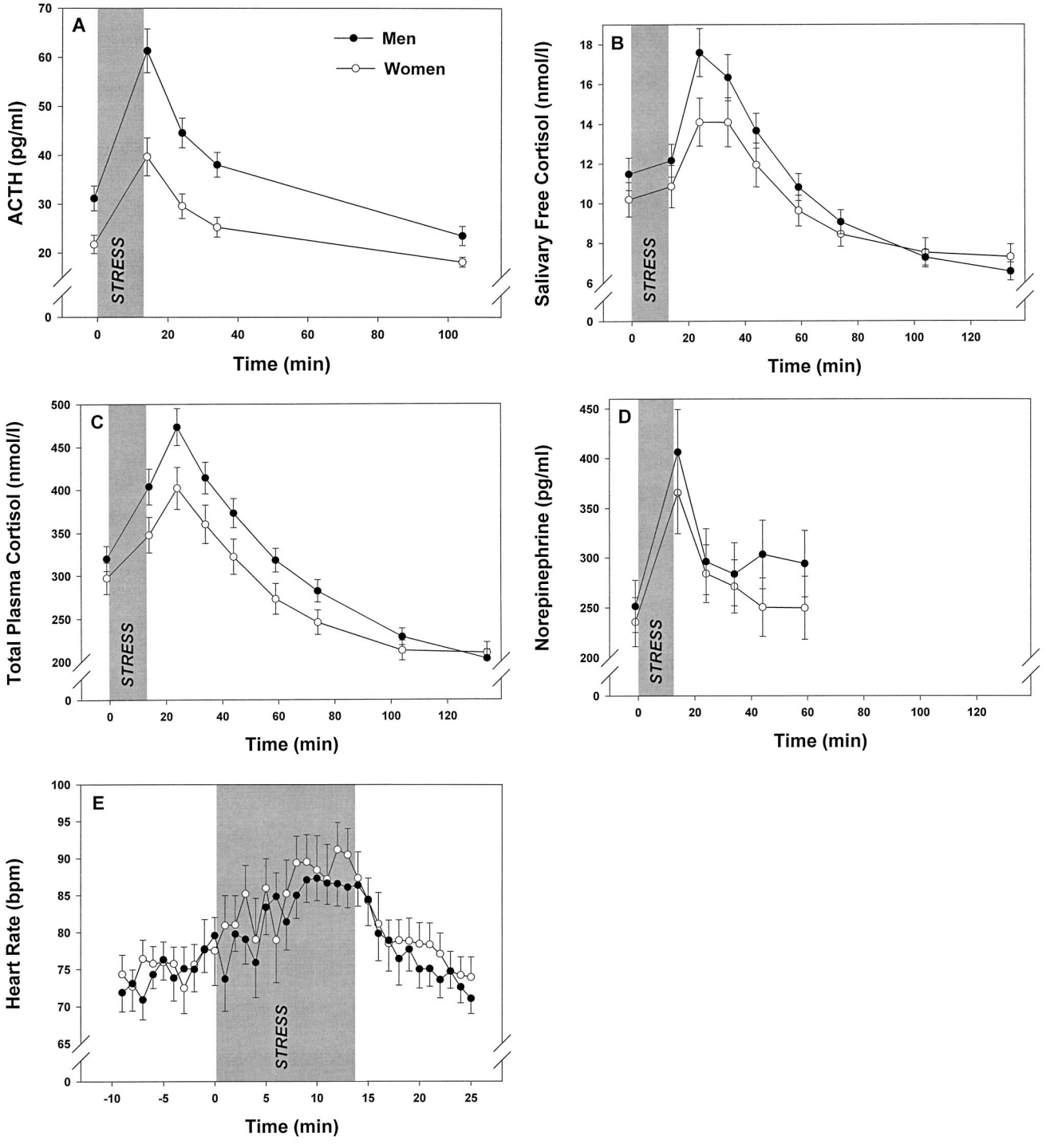

FIG. 1. Mean ACTH (A), salivary free cortisol (B), total plasma cortisol (C), norepinephrine (D), and heart rate (E) levels (±SEM) before and after stress (TSST) in placebo-treated subjects. The *shaded areas* indicate the period of stress exposure.

chols Institute, Bad Nauheim, Germany). Norepinephrine and epinephrine were assayed by high performance liquid chromatography, as previously described (16). Inter- and intraassay coefficients of variance were below 12% and 10%, respectively, for all analytes.

Heart rate

Heart rates were measured continuously at 1-min intervals with electrocardiogram precision employing wireless transmission (Sport Tester Profi, Polar Instruments, Gross-Gerau, Germany). Heart rate responses were computed from 10 min before stress exposition to 10 min after cessation of stress.

Statistical analyses

ANOVAs for repeated measures were used to analyze endocrine and heart rate responses to the stressor. To control for different baseline levels, hormone samples obtained directly before the stress exposition were treated as covariates. All reported results were corrected by Greenhouse-Geisser procedure where appropriate. Newman-Keuls *post-hoc*

tests were applied for significant effects. For all analyses, the significance level was $\alpha = 5\%$. Correlations were computed by Pearson product-moment correlations. Factor analyses (principal component, varimax oblique) and reliability analyses were employed to create the scale "stressfulness" based on items of the VAS. A χ^2 test was used to analyze whether the subjects were able to correctly identify the content of the received capsules. Changes in physical or psychological well-being were determined both for the total sample and for each sex separately by Kruskal-Wallis ANOVAs. The nominal α level was adjusted by Bonferroni correction for multiple comparisons. All results shown are the mean ± SEM.

Results

In the total group the psychosocial stress protocol caused significant endocrine, cardiovascular, and psychological responses. ACTH, salivary free cortisol, plasma total cortisol, and norepinephrine increased significantly, with 30–100% changes from baseline values. ACTH and norepinephrine concentrations peaked 1 min after cessation of the TSST, with continuously decreasing hormone concentrations thereafter (ACTH: $F = 96.22$; $P < 0.0001$; norepinephrine: $F = 28.15$; $P < 0.0001$). The epinephrine stress response did not quite reach statistical significance ($F = 3.34$; $P < 0.069$). Cortisol levels were highest 10 min after cessation of stress (free cortisol: $F = 81.17$; $P < 0.0001$; plasma total cortisol: $F = 106.88$; $P < 0.0001$). Maximum heart rate responses were observed between 5–15 min of stress exposure ($F = 13.82$; $P < 0.0001$). Correlations between cortisol and ACTH stress responses (expressed as areas under the response curves) were significant, with $r = 0.53$ (salivary cortisol *vs.* ACTH, $P < 0.001$) and $r = 0.61$ (total cortisol *vs.* ACTH, $P < 0.001$).

ANOVAs revealed significant sex differences for salivary free cortisol and ACTH stress responses (ACTH: $F = 7.60$; $P = 0.0041$; salivary free cortisol: $F = 2.98$; $P = 0.044$) and a trend for plasma total cortisol ($F = 2.28$; $P = 0.076$). Men showed significantly higher ACTH concentrations at 1, 10, 20, and 90 min as well as higher salivary free cortisol concentrations 10 and 20 min after cessation of stress (all $P < 0.05$). Norepinephrine, epinephrine, or heart rate responses did not differ between sexes (Fig. 1).

Stress exposure worsened mood in the total group ($F = 6.92$; $P < 0.002$). *Post-hoc* tests revealed that mood was decreased after stress compared to the two prestress measurements. Scores in the scales wakefulness *vs.* sleepiness and calmness *vs.* restlessness remained unchanged. No sex differences in mood were observed.

A factor analysis clustered seven items to the factor perceived stressfulness (task was strenuous, free speech was difficult, arithmetic task was difficult, stressful, novel, uncontrollable, and threatening). The reliability of the resulting factor was $\alpha = 0.90$ (Cronbach's α). Men and women differed significantly in perceived stressfulness of the TSST, with women reporting to be more stressed ($F = 8.37$; $P < 0.0051$; Fig. 2). There was no significant sex difference in the amount of perceived challenge or the perceived importance of individual performance.

DHEA- and placebo-treated subjects did not differ significantly in age, body mass index, or DHEA-S or androstendione levels before treatment (Table 1). As expected, the DHEA group had significantly higher DHEA-S levels (group by time effect: $F = 207.75$; $P < 0.0001$) and androstendione

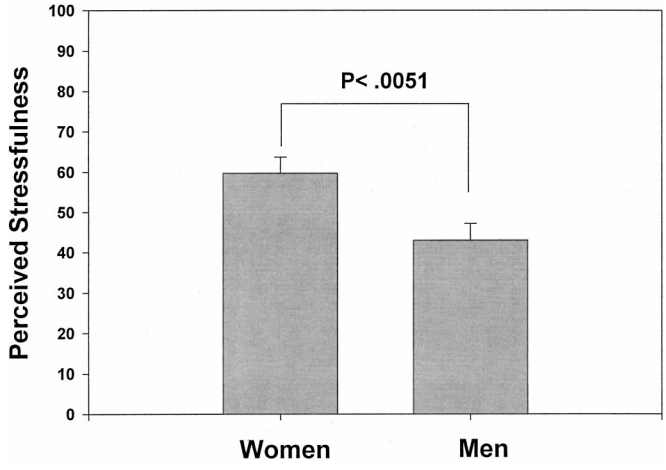

FIG. 2. Mean perceived stressfulness of the TSST in men and women.

TABLE 2. Number of subjects who "guessed" that they had received a DHEA capsule or placebo capsule, respectively

	Capsule 'guess'	
	Placebo	DHEA
Placebo group	24	7
DHEA group	26	11

$\chi^2_1 = 0.50$; P = NS.

levels (group by time effect: $F = 47.33$; $P < 0.0001$) after 2 weeks of treatment (Table 1). Analyses of estradiol levels revealed a significant sex difference ($F = 18.28$; $P < 0.0001$) and a group by time effect ($F = 4.36$; $P < 0.041$), with men showing higher estradiol levels before and after treatment. Due to replacement, the substituted group showed a marked increase in estradiol levels, whereas estradiol concentrations decreased slightly in the placebo group. Free testosterone was higher in men than in women before and after DHEA substitution ($F = 218.09$; $P < 0.0001$). Subjects were unable to identify correctly the received treatment ($\chi^2 = 0.50$; P = NS; Table 2).

Treatment with DHEA resulted in increased ACTH responses in women ($F = 6.98$; $P < 0.009$), with no change in men (Fig. 3). Salivary free cortisol and norepinephrine stress responses also tended to be enhanced in DHEA-treated subjects (P = NS). No changes were observed in total plasma cortisol and epinephrine responses (P = NS). DHEA treatment neither affected mood, physical or psychological well-being, nor perceived stressfulness of the TSST (all P = NS).

Discussion

In the past, few studies have investigated HPA responses to standardized psychosocial stress protocols in elderly individuals. Although significant HPA activations were obtained in two studies (13, 17), a third study failed to evoke similar stress responses (18).

The present results show that the applied psychosocial stress protocol (TSST) induces significant activation of the HPA axis and the sympathetic nervous system in elderly subjects, which resemble the responses observed in children and younger adults (11, 19). More important, this is the first study to report clear-cut sex differences in HPA responsive-

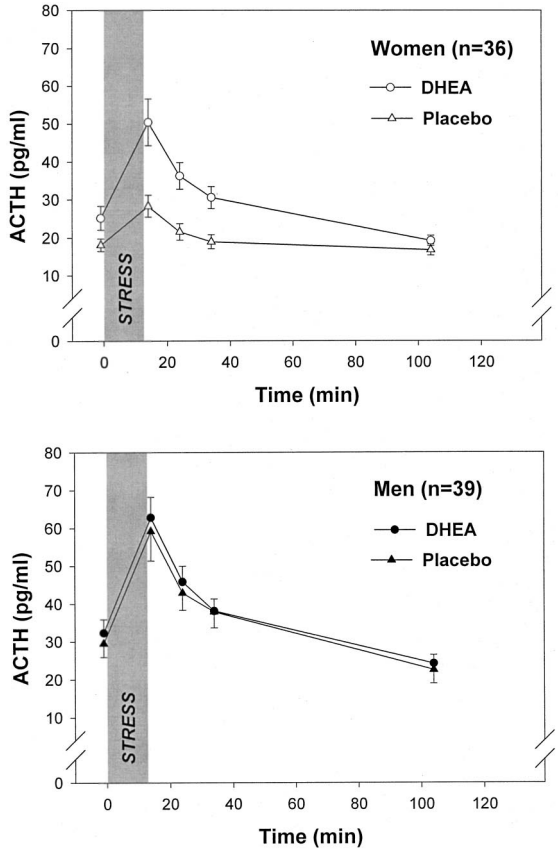

FIG. 3. ACTH levels (mean ± SEM) before and after TSST in DHEA or placebo-treated subjects. The *shaded areas* indicate the period of stress exposure.

ness to psychosocial stress in elderly individuals. In accord with previous results obtained in younger adults (7), elderly men showed higher ACTH and cortisol stress responses than age-matched postmenopausal women. This was rather surprising, because women reported that they were more stressed by the TSST than did men with a comparable level of need for achievement. As none of the other subjective ratings assessed in this study revealed any sex differences, it appears more likely that endocrine rather than psychological factors might be responsible for the observed HPA responses. One of the prime candidates for explaining sex differences in HPA stress responsiveness is obviously the gonadal steroids. Among them, estradiol exerts a strong stimulatory influence on the axis in several animal species (20–25), with important modulatory effects on mineralocorticoid and glucocorticoid receptors (26–30). Moreover, estradiol may directly enhance CRF gene transcription in the hypothalamus through binding to estrogen-responsive elements on the CRF gene (31). Testosterone, on the other hand, could exert similar effects after being metabolized to estrogens by aromatization in both brain and peripheral tissues (32–35). Although women appear to be more sensitive at the pituitary and adrenal levels (3–6), the higher testosterone and estradiol levels of elderly men may explain the enhanced ACTH and cortisol responses after suprapituitary stimulation.

Short term treatment with DHEA seems to increase the HPA response in women. In our study, DHEA-substituted women showed "male-like" endocrine stress profiles. The enhanced ACTH stress responses were probably caused by DHEA-induced elevations of estradiol levels in this group of women. However, other mechanisms could provide alternative explanations for the present observation. An enhanced ACTH stress response after DHEA treatment could be a consequence of the influence of DHEA and DHEA-S on the γ-aminobutyric $acid_A$ receptor system in the central nervous system (36–38). This may lead to increased secretion of vasopressin (39), which, in turn, acts synergistically with CRF on corticotrophs. Moreover, DHEA treatment did not alter mood or well-being, which is in line with previous findings of this laboratory (40–42).

In conclusion, marked sex differences in HPA responses to psychosocial stress persist across a wide age range. As in younger adults, elderly men showed higher HPA responsiveness than women to a public speaking and mental arithmetic task. In contrast to antiglucocorticoid effects observed in rodents, a brief treatment with DHEA appears to enhance the pituitary stress responses in women.

References

1. **Kitay JI.** 1963 Pituitary-adrenal function in the rat after gonadectomy and gonadal hormone replacement. Endocrinology. 7:253–260.
2. **Kitay JI.** 1961 Sex differences in adrenal cortical secretion in the rat. Endocrinology. 68:818–824.
3. **Roelfsema F, van den Berg G, Frölich M, et al.** 1993 Sex-dependent alteration in cortisol response to endogenous adrenocorticotropin. J Clin Endocrinol Metab. 77:234–240.
4. **Gallucci WT, Baum A, Laue L, et al.** 1993 Sex differences in sensitivity of the hypothalamic-pituitary-adrenal axis. Health Psychol. 12:420–425.
5. **Heuser IJ, Gotthardt U, Schweiger U, et al.** 1994 Age-associated changes of pituitary-adrenocortical hormone regulation in humans: importance of gender. Neurobiol Aging. 15:227–231.
6. **Peskind ER, Raskind MA, Wingerson D, et al.** 1995 Enhanced hypothalamic-pituitary-adrenocortical axis responses to physostigmine in normal aging. J Gerontol A Biol Sci Med Sci. 50A:M14–M20.
7. **Kirschbaum C, Wüst S, Hellhammer D.** 1992 Consistent sex differences in cortisol responses to psychological stress. Psychosom Med. 54:648–657.
8. **Kirschbaum C, Pirke KM, Hellhammer DH.** 1995 Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. Psychoneuroendocrinology. 20:509–514.
9. **Kirschbaum C, Klauer T, Filipp SH, Hellhammer DH.** 1995 Sex-specific effects of social support on cortisol and subjective responses to acute psychological stress. Psychosom Med. 57:23–31.
10. **Kirschbaum C, Schommer N, Federenko I, et al.** 1996 Short-term estradiol treatment enhances pituitary-adrenal axis and sympathetic responses to psychosocial stress in healthy young men. J Clin Endocrinol Metab. 81:3639–8643.
11. **Kirschbaum C, Pirke KM, Hellhammer DH.** 1993 The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 28:76–81.
12. **Zung WW, Richards CB, Short MJ.** 1965 Self-rating depression scale in an outpatient clinic. Further validation of the SDS. Arch Gen Psychiatry. 13:508–515.
13. **Gotthardt U, Schweiger U, Fahrenberg J, Lauer CJ, Holsboer F, Heuser I.** 1995 Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am J Physiol. 268:R865–R873.
14. **Steyer R, Schwenkmezger P, Notz P, Eid M.** 1994 Testtheoretische Analysen des Mehrdimensionalen Befindlichkeitsfragebogens (MDBF). Diagnostica. 40:320–328.
15. **Dressendörfer RA, Kirschbaum C, Rohde W, Stahl F, Strasburger CJ.** 1992 Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. J Steroid Biochem Mol Biol. 43:683–692.
16. **Smedes F, Kraak JC, Poppe H.** 1982 Simple and fast solvent extraction system for selective and quantitative isolation of adrenalin, noradrenalin and dopamine for plasma and urine. J Chromatogr. 231:25–39.
17. **Seeman TE, Singer B, Charpentier P.** 1995 Gender differences in patterns of HPA axis response to challenge: Macarthur studies of successful aging. Psychoneuroendocrinology. 20:711–725.
18. **Nicolson N, Storms C, Ponds R, Sulon J.** 1997 Salivary cortisol levels and stress reactivity in human aging. J Gerontol A Biol Sci Med Sci. 52A:M68–M75.

19. **Buske-Kirschbaum A, Jobst S, Wustmans A, Kirschbaum C, Rauh W, Hellhammer D.** 1997 Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom Med. 59:419–426.
20. **Bossmar T, Forsling M, Akerlund M.** 1995 Circulating oxytocin and vasopressin is influenced by ovarian steroid replacement in women. Acta Obstet Gynecol Scand. 74:544–548.
21. **Lesniewska B, Miskowiak B, Nowak M, Malendowicz LK.** 1990 Sex differences in adrenocortical structure and function. XXVII. The effect of ether stress on ACTH and corticosterone in intact, gonadectomized, and testosterone- or estradiol-replaced rats. Res Exp Med (Berl). 190:95–103.
22. **Manin M, Delost P.** 1984 Dynamic measure of production rate of cortisol in the mature guinea-pig in response to the stress of anesthesia: effect of estradiol. Steroids. 43:101–110.
23. **Norman RL, Smith CJ, Pappas JD, Hall J.** 1992 Exposure to ovarian steroids elicits a female pattern of plasma cortisol levels in castrated male macaques. Steroids. 57:37–43.
24. **Viau V, Meaney MJ.** 1991 Variations in the hypothalamic-pituitary-adrenal response to stress during the estrous cycle in the rat. Endocrinology. 129:2503–2511.
25. **Xiao E, Xia L, Shanen D, Khabele D, Ferin M.** 1994 Stimulatory effects of interleukin-induced activation of the hypothalamo-pituitary-adrenal axis on gonadotropin secretion in ovariectomized monkeys replaced with estradiol. Endocrinology. 135:2093–2098.
26. **Burgess LH, Handa RJ.** 1992 Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. Endocrinology. 131:1261–1269.
27. **Carey MP, Deterd CH, de Koning J, Helmerhorst F, De Kloet ER.** 1995 The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat. J Endocrinol. 144:311–321.
28. **Peiffer A, Lapointe B, Barden N.** 1991 Hormonal regulation of type II glucocorticoid receptor messenger ribonucleic acid in rat brain. Endocrinology. 129:2166–2174.
29. **Redei E, Li L, Halasz I, McGivern RF, Aird F.** 1994 Fast glucocorticoid feedback inhibition of ACTH secretion in the ovariectomized rat: effect of chronic estrogen and progesterone. Neuroendocrinology. 60:113–123.
30. **Turner BB.** 1992 Sex differences in the binding of type I and type II corticosteroid receptors in rat hippocampus. Brain Res. 581:229–236.
31. **Vamvakopoulos NC, Chrousos GP.** 1993 Evidence of direct estrogenic regulation of human corticotropin-releasing hormone gene expression. Potential implications for the sexual dimorphism of the stress response and immune/inflammatory reaction. J Clin Invest. 92:1896–1902.
32. **Chowen JA, Argente J, Vician L, Clifton DK, Steiner RA.** 1990 Pro-opiomelanocortin messenger RNA in hypothalamic neurons is increased by testosterone through aromatization to estradiol. Neuroendocrinology. 52:581–588.
33. **Finkelstein JS, Whitcomb RW, O'Dea LS, Longcope C, Schoenfeld DA, Crowley Jr WF.** 1991 Sex steroid control of gonadotropin secretion in the human male. I. Effects of testosterone administration in normal, and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 73:609–620.
34. **Weissberger AJ, Ho KK.** 1993 Activation of the somatotropic axis by testosterone in adult males: evidence for the role of aromatization. J Clin Endocrinol Metab. 76:1407–1412.
35. **Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ.** 1994 Effects of endogenous testosterone and estradiol on sexual behavior in normal young. J Clin Endocrinol Metab. 78:711–716.
36. **Majewska MD.** 1992 Neurosteroids: endogenous bimodal modulators of the GABA-A receptor. Mechanism of action and physiological significance. Prog Neurobiol. 38:379–395.
37. **McEwen BS.** 1991 Non-genomic and genomic effects of steroids on neural activity. Trends Pharmacol Sci. 12:141–147.
38. **Robel P, Baulieu E-E.** 1994 Neurosteroids: biosynthesis and function. Trends Endocrinol Metab. 5:1–8.
39. **Sladek CD, Armstrong WE.** 1987 γ-Aminobutyric acid antagonists stimulate vasopressin release from organ-cultured hypothalamo-neurophyseal explants. Endocrinology. 120:1576–1580.
40. **Wolf OT, Neumann O, Hellhammer DH, et al.** 1997 Effect of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. J Clin Endocrinol Metab. 82:2363–2367.
41. **Wolf OT, Naumann E, Hellhammer DH, et al.** Effects of dehydroepiandrosterone (DHEA) replacement in elderly men on event related potentials (ERP's), memory, and well-being. J Gerontol. In press.
42. **Wolf OT, Kirschbaum C, Hellhammer DH, Born J, Fehm HL.** 1997 A single administration of dehydroepiandrosterone (DHEA) does not enhance memory performance in young healthy adults, but immediately reduces cortisol levels. Biol Psychiatry. 42:845–848.