Salivary Cortisol Levels and Stress Reactivity in Human Aging

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Background. While homeostatic mechanisms are generally believed to become less efficient in the aging organism, evidence for changes in hypothalamic-pituitary-adrenal function is inconclusive. Previous studies report higher, lower, or unchanged basal cortisol levels in human aging. Delayed recovery of glucocorticoids to baseline following stress exposure has been observed in aging rats, but the generalizability of these findings to humans remains unclear.

Methods. Salivary-free cortisol was measured at home and in response to a laboratory speech task in 56 healthy men and women in three age groups (range 43–86 yr).

Results. Higher basal cortisol levels were observed in older age groups. Gender, recent life stress, and current distress showed no relationship to basal levels. The magnitude of cortisol responses to the speech task differed by age, with the smallest responses in the oldest group. This pattern was robust in men, with the youngest subjects (40–59 yr) showing both the largest and the most prolonged responses. While women > 70 yr were least likely to show any response, other analyses failed to show age effects on reactivity in women, perhaps because anticipatory baseline elevations limited subsequent cortisol response.

Conclusions. Results indicate moderate increases in basal cortisol levels, but do not support the hypothesis that cortisol responses to a stressor increase in magnitude or duration during normal human aging. Gender differences in stress reactivity warrant further investigation.

The hypothalamic-pituitary-adrenal (HPA) axis plays a vital role in the regulation of physiological processes (1). Although it is generally accepted that homeostatic mechanisms become less efficient in the aging organism, evidence for changes in HPA function in the course of normal human aging is mixed. In the majority of studies, basal levels of cortisol show little change (2–11); a few studies, however, report significantly higher (12,13) or lower (14–18) basal cortisol levels in older subjects. These results are thought to be due to changes in circadian rhythmicity and sleep processes, cortisol secretion is particularly likely to show age-related increases in the evening and the early hours of the night (19,20).

Challenge tests assess the functional integrity of the feedback system at various levels of the axis. Results with respect to human aging have recently been reviewed (21). Adrenocorticotropic hormone (ACTH) challenge studies have shown no significant age differences in initial cortisol response. Following administration of dexamethasone (DEX), a synthetic glucocorticoid, cortisol responses are either unchanged or increased in older subjects. Corticotropin releasing hormone (CRH) infusion produces similar ACTH and cortisol responses in older and younger subjects, although the timing of the peak response may vary. Combined DEX/CRH challenge tests may reveal more subtle changes; using this procedure, a recent study found age-related increases in HPA activity, especially in women (22).

Cortisol responses to hormonal or pharmacologic challenges are not necessarily correlated with responses to stressors, nor do all classes of stressors have the same effect. In a study in young adults, for example, males and females did not differ in cortisol response to CRH administration or to physical stressors, but males responded to psychosocial stressors with cortisol elevations twice as high as those observed in females (23). As another example, cortisol responses to CRH challenge and to a simulated driving task were uncorrelated in a study of healthy 70-year-olds (24). Particularly under circumstances in which individual differences in appraisal and coping processes are brought into play, low correlations between the functional capacity of the HPA system and the observed response to experimental stressors can be expected. To the extent that such stressors can serve as models for how individuals respond to real-life stress, they are an important complement to biological challenge tests. Surprisingly little research has been done on age-related changes in cortisol response to acute physical or psychological stressors in humans. Age appears to have no effect on cortisol response to cold exposure (16) or to the cold pressor test (25). The cortisol response to insulin-induced hypoglycemia is also similar in young and elderly subjects (5). Older patients showed increased cortisol responses to trauma in one study (26), but not in another (27). The majority of challenge or reactivity studies have focused on the response amplitude only. In rats, however, it appears that aging has little effect on the rate or amplitude of the initial glucocorticoid response, but is associated with delayed post-stress recovery to basal levels (28,29). Delayed termination of HPA activity following stress is thought to reflect deficits in glucocorticoid feedback regulation (30).
The generalizability of the above findings in rodents to humans remains unclear.

The goals of the current study were twofold. The first was to clarify whether basal free cortisol levels, measured in saliva, change in the course of normal human aging. The second goal was to determine whether there are age-related differences in patterns of acute cortisol reactivity to a psychosocial stressor, a laboratory speech task. Differences in the magnitude as well as the time course of the cortisol response were examined. Because there is considerable evidence for gender differences in cortisol reactivity (22,23) and at least one report of differences in basal levels (17), the effects of gender (both independently and in relation to age) were specifically assessed. We also examined possible influences on basal cortisol measures of recent life stress, psychological symptomatology, coping style, and body mass, and the relationship between emotional state and cortisol response to the speech task.

METHODS

Subjects

Subjects were selected in three age groups (I: 40–59 yr, II: 60–69 yr, III: ≥ 70 yr), with approximately equal numbers of males and females. Sixty-four subjects from a pool of volunteers for studies of cognitive changes in aging were approached by telephone. Of these, four were excluded due to diabetes, thyroid abnormalities, or use of medications that could influence cortisol levels; two refused; and two could not participate on the planned dates. The remaining subjects reported being in good health.

Age group I consisted of 6 men and 10 women, ranging in age from 43 to 58 yr (mean = 50 yr). Three subjects smoked cigarettes. Four of the women had regular menstrual cycles, one of whom used oral contraceptives; the remaining six women were postmenopausal. Age group II included 10 men and 10 postmenopausal women, ranging in age from 62 to 69 yr (mean = 65.5 yr). Four subjects smoked. Age group III originally included 10 men and 10 postmenopausal women; one male subject was later excluded from the analysis due to abnormal cortisol values (see Statistical Analysis, below). The remaining 19 subjects ranged in age from 70 to 86 yr (mean = 77.7 yr). Two subjects in age group III smoked. In the total sample of 55 subjects, mean educational level, measured on an 8-point scale from primary school to higher vocational training and university, was 3.9 (range 1–8), with no significant age group [F(2,49) = .95, p = .30] or gender [F(1,49) = 1.71, p = .20] differences. Body mass index (BMI = kg/m², calculated from self-reported weight and height) ranged from 18.4 to 38.2 (mean = 24.6) and did not differ by age group [F(2,49) = 1.22, p = .30] or by gender [F(1,49) = .01, p = .92].

Assessment of Basal Cortisol Levels

Subjects were visited at home, where informed consent was obtained, questionnaires completed, and instructions given for saliva sample collection. At prearranged times in the morning (8 a.m.), late afternoon (4 p.m.), and late evening (9 p.m.) on two consecutive days, subjects collected saliva samples with a cotton dental roll, which was stored in a capped plastic vial ("Salivette," Sarstedt, Rommelsdorf, Germany). Subjects stored samples in their home freezers until coming to the laboratory, where uncentrifuged samples were frozen at -20 °C until analysis.

Assessment of Stress Reactivity

In the week following basal cortisol sampling at home, cortisol and emotional responses to an experimental stressor were measured in the laboratory during a speech task (Stress-Inducing Speech Task, SIST), in which subjects were asked to prepare (10 min) and deliver (5 min) a speech concerning their best and worst personal characteristics. Subjects were told that their presentations would be videotaped for later analysis by a team of psychologists. This task has been shown to induce cortisol elevations within 15 min (31).

The SIST took place between 3 p.m. and 5 p.m. Cortisol levels are generally fairly stable at this time of day, with no significant change due to circadian rhythm effects within the 2-hr interval. Saliva was collected before subjects received standardized instructions concerning the SIST (t0), immediately after the SIST (t20: 20 min after t0), and twice (t40, t60) in a recovery period, during which subjects read neutral magazines. At the same time points, emotional reactivity to the SIST was assessed with 13 mood items presented as 10 cm visual analogue scales. The items nervous, anxious, tense, irritated, dejected, worried, and disappointed formed the negative affect (NA) scale (Cronbach’s alpha = .74); the items happy, confident, enthusiastic, satisfied, exhilarated, and relieved formed the positive affect (PA) scale (alpha = .81). Item scores were summed and divided by the number of items to produce a score for each mood scale ranging from 0 to 10.

Assessment of Life Stress and Psychological Characteristics

The following questionnaires were completed to assess anxiety, depression, stress, and coping:

Anxiety: Trait anxiety was measured with the Dutch version of the State-Trait Anxiety Inventory (32).

Depression: Depressive symptomatology was assessed with the Dutch version of the Zung self-report scale (33).

Life events: The LTE-Q is a list of 12 major life events, such as the death of a family member, divorce, or serious illness (34). Subjects indicated whether each type of event had occurred in the past year and, if so, in which month.

Chronic stress: The Groningen List of Long-term Difficulties (GLLM) is a questionnaire concerning chronic stress in domains such as work, housing, finances, physical health, and social relations. Most of the items are scored on 4-point scales (from 1 = no difficulty to 4 = severe difficulties), with a smaller number of problems scored as present/absent (35).

Perceived stress: The Perceived Stress Scale (PSS, 10-item version) (36), is a global measure of the extent to which individuals appraise their lives in the past month as stressful, reflecting aspects such as unpredictability, uncontrollability, and overload.

Coping: Habitual coping style was measured with the Utrecht Coping List (37). The 47 items are grouped into seven subscales: problem-focused, palliative behaviors/
Biochemical Analysis

Salivary cortisol has been shown to be highly correlated with plasma or serum levels; it is largely unbound and thus represents the "free," biologically active fraction of the hormone (38). Salivary cortisol levels were determined in duplicate by direct radioimmunoassay, using 125I-cortisol (Farmos Diagnostica, Finland) and antiserum made against the 3-CMO-BSA conjugate. The lower detection limit of the assay was .33 nmol/l, with a mean intra-assay coefficient of variation of 4.8%. Multiplication by 36.2 converts cortisol values from nmol/l to ng/dl.

Statistical Analysis

Data from one subject (male, 79 yr) were excluded from the analysis because cortisol levels in all 10 samples (ranging from 64 to 214 nmol/l) were far outside the normal range, exceeding levels reported for Cushing's disorder. Cortisol values were transformed to natural logarithms to normalize the distributions, which were positively skewed in samples collected in the laboratory, and to meet requirements of homoscedasticity for the statistical models used.

Cortisol levels in samples collected at home at the same time of day on two consecutive days did not significantly differ (paired t-tests; p-values all > .05); the mean of the two measures was therefore used in the analysis of basal secretory patterns. Multivariate analysis of variance (MANOVA) was used to test main and interaction effects of the factors age, gender (three groups: I, 40-59 yr; II, 60-69 yr; III, ≥ 70 yr) and gender. Contributions of body mass, life stress, anxiety, depression, and coping measures to the variance in total cortisol secretion (defined as the sum of 8 a.m., 4 p.m., and 9 p.m. levels) were estimated, together with the effects of age as a continuous variable, by forward stepwise multiple regression. To test whether cortisol levels might increase exponentially in the oldest subjects, a quadratic term for age was included in the equation.

Cortisol peak and mean responses to the SIST were defined as changes from prespeech (t0) baseline levels. Age- and gender-related differences in peak response were tested with MANOVA. Age and gender effects on the time course of responses to the SIST were tested with repeated measures MANOVA, using Hotelling's probability estimates. The influence of anticipatory elevation in lab baseline cortisol on peak and mean responses was tested with forward stepwise multiple regression.

Statistical tests were performed with SPSS, Macintosh version. Unless otherwise noted, significance levels are based on two-tailed tests, with p ≤ .05 considered significant.

RESULTS

Basal Cortisol Levels

As shown in Figure 1, increasing age was associated with higher salivary cortisol levels at all three times of day. Repeated measures MANOVA revealed a statistically significant main effect for age [F(2,49) = 5.07, p = .01], but not for either gender [F(1,49) = .10, p = .75] or the Age by Gender interaction [F(2,49) = .05, p = .95]. Time of day had a strong effect on cortisol levels [F(2,49) = 1.36, p ≤ .001], reflecting the known circadian secretory pattern. A similar diurnal pattern was observed in all three age groups and in both sexes: Time of Day by Age [F(2,49) = 1.11, p = .36], Time of Day by Gender [F(2,49) = .30, p = .74], and the three-way interaction term [F(2,49) = .09, p = .99] were all nonsignificant.

Over all subjects, age (yr) was significantly correlated with basal cortisol at each time of day (8 a.m.: r = .30, p ≤ .05; 4 p.m.: r = .31, p < .05; 9 p.m.: r = .39, p < .01). We next examined whether the age effect might reflect differences in stress, distress, or coping measures. The three age groups did not differ in number of recent life events or perceived stress, but chronic difficulties tended to decrease with age, with total scores on the GLLM Likert-scale items averaging 23.24, 20.75, and 20.05 in age groups I, II, and III, respectively (Kruskal-Wallis test, p = .06). No differences were found on depression, anxiety, and coping measures, with the exception of the coping style "expression of emotions/anger," which decreased with age (means of 6.87, 5.75, and 5.16 for groups I, II, and III, respectively, Kruskal-Wallis test, p = .05). Next, forward stepwise multiple regression was performed with total cortisol as the dependent variable and age, gender, body mass index, number of recent life events, perceived stress, chronic difficulties, depression, anxiety, and scores on the seven coping factors as independent variables. Of these, only age was a significant predictor of total cortisol (R2 = .19, p < .001); the quadratic age term was nonsignificant, indicating that the age effect was linear.

To test whether the same pattern held true for both sexes,
we repeated the regression analysis for males and females separately. In males, age was again the only significant predictor of total cortisol ($R^2 = .23$, $p < .001$). In females, both age ($\beta = .533$, $p = .0007$) and avoidant coping ($\beta = -.607$, $p = .0002$) were significant predictors of baseline levels, together explaining 54% of the variance in total cortisol ($p \leq .0001$).

**Reactivity to the Speech Task**

**Cortisol responses.** — Table 1 summarizes cortisol responses measured in the laboratory. Prespeech baseline was elevated in comparison to 4 p.m. home level in 32 of the 55 subjects (means for the entire sample of 4.39 nmol/l in the laboratory vs 3.46 nmol/l at home; Wilcoxon test, $p \leq .05$), probably due to the novelty of the laboratory setting or to anticipatory anxiety. Neither lab baseline nor anticipatory response (change in lab baseline relative to home level), however, differed significantly by age or by gender.

The average peak response represented a 37% increase over laboratory baseline and a 77% increase over home level. Peak response differed by age [$F(2,49) = 3.80$, $p \leq .03$]; furthermore, although gender had no main effect [$F(1,49) = 2.89$, $p \leq .10$], there was a significant interaction between age and gender [$F(2,49) = 5.85$, $p \leq .005$]. Post-hoc examination of the age effect (one-way analysis of variance) indicated that, while no two groups were statistically significantly different from one another, the oldest group had the lowest cortisol peaks relative to the two younger groups combined (based on separate variance estimates, 48.6 df, $r$-value $= -2.54$, $p = .014$).

Using a more stringent definition of ‘response’ [peak increment of > 2.76 nmol/l (39)], we found no difference in the percentage of responders in each age group (Chi-square $= .62$, $p = .73$). The percentage of complete nonresponders (subjects with no increase in cortisol levels above lab baseline), on the other hand, increased with age (Chi-square $= 6.63$, $p \leq .02$).

The mean cortisol response is a measure that combines both magnitude and duration; based on three samples obtained at equal (20 min) time intervals, it approximates an area-under-the-curve measure. MANOVA results indicated a significant effect of age on mean response [$F(2,49) = 4.16$, $p \leq .02$]; here, as with peak response, gender had no main effect [$F(1,49) = 3.03$, $p \leq .09$], but there was a significant Age by Gender interaction [$F(2,49) = 4.81$, $p \leq .01$]. Gender differences in the age effect are shown in Figure 2. In men, but not in women, a pattern of decreasing response to the SIST with age can be observed.

**Time course.** — The results of the repeated measures MANOVA confirmed age [$F(2,49) = 4.16$, $p \leq .02$] and age by gender [$F(2,49) = 4.81$, $p \leq .01$] differences in the overall cortisol response, with no significant effect of gender alone [$F(1,49) = 3.03$, $p = .09$]. With respect to the time course of the response, a significant effect of time [$t(20, t40, t60; F(2,48) = 4.43$, $p \leq .02$] and a Gender by Time interaction effect [$F(2,48) = 5.66$, $p \leq .006$] were found. Age, in contrast, had no significant effect on the temporal patterning of the cortisol response [$F(4,94) = .42$, $p = .80$], either alone or in interaction with gender [$F(4,94) = 1.16$, $p = .34$]. In Figure 3, it is evident that the cortisol response to the SIST tended to peak later in men than in women. With a late response defined as the observed cortisol peak at t40 or t60, 14 of the 25 men compared to 7 of the 30 women showed a late response (Chi-square $= 6.17$, $p \leq .05$).

**Effects of anticipatory cortisol elevation.** — Next, we evaluated the possibility that anticipatory changes in cortisol laboratory baseline, as described above, may have influenced the subsequent response to the SIST, possibly explaining or interacting with age effects. Across all subjects, a larger anticipatory response was associated with a smaller mean SIST response ($r = -.35$, $p \leq .01$); peak response also tended to be lower, although not significantly so ($r = -.25$, $p < .10$). Home levels at 4 p.m., on the other hand, showed no association with mean ($r = -.06$) or peak ($r = .03$) responses.

Since MANOVA results had already shown that age effects on cortisol responses were modified by gender, forward stepwise regressions were performed separately for male and female subsamples. Here, a new variable (Antici-

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**Table 1. Cortisol Response (nmol/l) to a Speech Task by Age Group and Gender**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Subjects</th>
<th>t0 Baseline (SD)</th>
<th>Peak* (SD)</th>
<th>High Response†</th>
<th>Nonresponse‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>I: 40–59 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>3.24 (.75)</td>
<td>3.33 (1.79)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>4.86 (2.53)</td>
<td>0.23 (2.40)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>II: 60–69 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>4.04 (1.65)</td>
<td>1.14 (2.54)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>3.55 (1.30)</td>
<td>2.34 (3.20)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>III: 70 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>6.24 (7.17)</td>
<td>1.64 (3.17)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>4.14 (1.34)</td>
<td>0.09 (1.14)</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>4.39 (3.27)</td>
<td>1.32 (2.63)</td>
<td>12</td>
<td>22</td>
</tr>
</tbody>
</table>

*Maximum cortisol change relative to baseline.
†Peak > 2.76 nmol/l.
‡Peak < 0 nmol/l.
Figure 2. Cortisol response to the speech task (SIST), averaged over t20, t40, and t60, in each age group, plotted separately for men, A, and for women, B. See legend for Figure 1 for further explanation.

A different picture emerged for women. Here, only the anticipatory response had a significant negative effect, which did not differ as a function of age, on both mean response ($R^2 = .23, p = .01$) and peak response ($R^2 = .19, p = .05$). Cortisol elevation in anticipation of the speech task thus appears to have limited subsequent response.

Emotional responses. — To determine whether subgroup differences in cortisol response to the SIST may have reflected different patterns of emotional response to the task, we first tested the significance of changes in negative (NA) and positive affect (PA) during the SIST with repeated measures MANOVA. Over all subjects, significant changes in NA were observed over the four assessments [$F(3,47) = 4.99, p = .004$]. NA tended to peak immediately after the speech performance and to decline to its lowest level by the end of the recovery period (means of 1.35, 1.88, 1.38, and 1.17 at t0, t20, t40, and t60, respectively). For PA, changes over time approached significance [$F(3,47) = 2.31, p = .09$], with the lowest ratings prior to the SIST, rising after the task and then remaining fairly stable throughout the recovery period (means of 4.46, 5.07, 5.07, and 5.20 at t0, t20, t40, and t60, respectively). Individual differences in overall NA levels were unrelated to age [$F(2,47) = 1.48, p = .24$], gender [$F(1,49) = .28, p = .60$], or their interaction [$F(2,49) = .10, p = .90$]. Similar nonsignificant results were obtained for PA. More importantly, within-subject patterns of change in NA and PA over time did not differ significantly in males vs females or among the three age groups, nor was the three-way (Time × Age × Gender) interaction statistically significant. Thus, age or gender differences in emotional response to the SIST do not appear to explain the effects of these variables on cortisol responses. Indeed, we found no evidence for an association between emotional state and cortisol response. Spearman correlations between mean levels of NA during the SIST with peak (rho
significant, as were those between mean PA with peak (rho = .08) and mean (rho = .06) cortisol responses.

DISCUSSION

Basal Cortisol

This study provides evidence for age-related increases in basal cortisol levels, remaining within the normal range, in both males and females. This finding is consistent with the results of some recent studies, but not with many others that have reported no effect of aging on basal HPA activity. A number of features of the current design may explain why age effects were demonstrated. Firstly, it appears that age differences in HPA activity are more likely to be found when samples include individuals older than 70 yr (40); our sample covered a relatively wide age range, with one-third of the subjects older than 70. However, while post-hoc comparisons showed a significant difference between the > 70 yr group and the combined younger groups only, regression analysis suggested that the age effect on basal cortisol was more or less linear over the entire sample. Secondly, discrepancies in the results of previous studies may be due to differences in the way cortisol was measured. Depending on whether cortisol is determined in plasma, urine, or saliva samples and whether total levels, free levels, or metabolites are assessed, different results may be obtained, even in the same subjects (41,42). In particular, total cortisol levels can be misleading if, for example, there are individual differences in level or activity of cortisol binding globulin. This, in addition to the evidence that it is the biologically active hormone fraction, makes free cortisol the measure of choice. Salivary free cortisol has the additional advantage of easy, stress-free measurement; this enabled us to obtain repeated samples at different times of day in the home environment, which may have provided a more reliable estimate of basal levels.

We found no difference in basal cortisol levels between males and females at any age. With the exception of reports of higher 4 p.m. salivary cortisol levels in men (43) and higher cortisol in old women than in old men (17), there appears to be little evidence for significant gender differences in basal levels in healthy subjects. Basal cortisol levels did not appear to be influenced by previous stress exposure or psychological distress. An avoidant coping style, characterized by a tendency to avoid stressful situations and let events take their own course (37), was associated with significantly lower basal cortisol levels in women. We have no explanation for this finding and suggest that it be interpreted with caution, given the number of independent variables in the regression equation relative to the number of subjects. Two additional factors should be considered with respect to possible psychosocial influences. Firstly, subjects in this study were healthy volunteers, with limited variability in measured life events or psychological symptomatology. Secondly, only recent life events, chronic difficulties, and perceived stress were assessed, whereas stress exposure over the lifetime might be expected to have greater cumulative effects on HPA axis regulation. Although difficult to conduct, prospective studies of the effects of chronic stress in aging humans would be informative.

What are the clinical implications of increased basal cortisol secretion with aging? In the current study, observed elevations in cortisol with age were moderate, with total levels in the oldest group on average 38% higher than those in the youngest group. Clearly, age-related changes are not necessarily pathological. Mild cortisol elevation could, for example, simply reflect normal changes in sleep patterns with aging. On the other hand, it has been postulated (20,29) that age-related changes in HPA activity may ultimately be markers of dysfunction in higher central nervous centers, including the hippocampus, hypothesized to be involved in the cognitive decline often observed in human aging. In addition to evidence from animal models, results from studies in humans point to possible detrimental effects of even slight increases in cortisol levels over time. For example, in a recent study in which basal cortisol levels were prospectively monitored over several years in healthy elderly, a pattern of increasing levels over time, within the normal range, was associated with a decline in specific cognitive functions (44). Such findings underscore the need for longitudinal studies in both healthy and patient populations.

Cortisol Reactivity

The magnitude of total and peak cortisol responses to the speech task varied in the three age groups, with the oldest subjects (> 70 yr) tending to show the smallest responses. These results contrast with those of Gotthardt et al. (45), who found greater cortisol responses to a cognitive challenge in older (> 60 yr) vs younger (< 30 yr) subjects. The current finding is also unexpected in light of results of recent studies showing increased reactivity to hormonal (22) and pharmacologic (46) challenges in older subjects. While the age-associated elevation in basal cortisol measured at home could theoretically result in diminished acute reactivity, as has been suggested in depression (45), we found no relationship between 4 p.m. home levels and either peak or mean response to the SIST. However, anticipatory elevation in cortisol levels prior to the speech task, in relation to home levels at the same time of day, complicates the interpretation of the results. While the pattern of decreasing cortisol response to the speech task with increasing age was confirmed for men, in whom anticipation appeared to have a negligible effect, women with high anticipatory elevation had blunted cortisol responses to the speech task. It is impossible to assess the extent to which anticipatory responses may have obscured or confounded the results of previous laboratory stress reactivity studies, since home basal levels have very rarely been measured [see (47) for an illuminating exception]. Without these, one is unable to determine whether lengthier acclimation procedures do indeed have the desired effect of stabilizing baseline cortisol.

Despite the statistically significant age effect on reactivity, it is important to note the marked individual differences, particularly in the oldest group; while the majority (12 of the 19 subjects, including 8 of the 10 women) showed no post-stress cortisol elevation, high (> 2.76 nmol/l) peak responses were observed in three individuals, including the oldest subject (male, 86 yr). Another elderly male (79 yr)
was excluded from the analysis due to consistent, abnormally high cortisol levels. Increasing heterogeneity in HPA activity (either basal or stimulated), even in the absence of changes in mean levels, may reflect vulnerability toward dysfunction in human aging (24, 48).

Age effects interacted with gender; in particular, men in the youngest age group (40–59 yr) showed relatively large cortisol responses, which also tended to peak later in time, and the oldest women, as mentioned above, were the least likely to show any response to the SIST. Greater cortisol reactivity to psychosocial stress in males compared to females has previously been reported in young adults (23) and in human neonates (49), but not, to our knowledge, in middle-aged or older subjects. In other studies, healthy elderly women have been reported to show larger cortisol responses to CRH administration (17) and to a combined dexamethasone suppression/CRH-stimulation test (22) than men. Gender effects therefore warrant further investigation. In addition, possible effects of estrogen replacement on salivary cortisol responses to stress should be examined (50–52); we did not have sufficiently reliable information on estrogen treatment to address this issue.

With respect to the hypothesis that aging is associated with delayed post-stress recovery of cortisol to basal levels, small or absent responses to the SIST in many of the subjects preclude definite conclusions about response duration. In this regard, it is important to note that the amplitude and duration of the responses in the youngest group of men were pronounced, similar to those observed in previous studies employing the same stressor (31). Nevertheless, different types of psychosocial challenges may be needed to reveal age differences in HPA system recovery from acute stress. In a pilot study of ACTH and cortisol responses to a driving simulation test, for example, healthy older subjects did show a prolonged post-stress elevation of cortisol levels compared to younger subjects [Seeman et al., cited in (21)], while Gotthardt et al. (45) found only slightly delayed cortisol recovery in old vs young subjects following a cognitive challenge. In addition, more frequent cortisol sampling throughout stressor exposure and recovery may be necessary to resolve subtle age-related differences.

Although age and gender may have influenced the subjective experience of the speech task, we found no differences in emotional responses or in trait characteristics that would support this hypothesis. Future studies with measures of cortisol and ACTH responses to CRH challenge and psychosocial stressors in the same subjects may help clarify whether age-related differences in stress reactivity reflect functional changes in the HPA axis and, if so, at what level.

Conclusion

In summary, our study provides evidence for age-dependent increases in basal HPA activity, as reflected in salivary cortisol secretion; the mechanisms underlying such changes and their significance in healthy human subjects remain to be clarified. The hypothesized delay in recovery of cortisol to basal levels following acute stress was not supported. In general, older subjects showed decreased rather than increased cortisol responses to an acute stressor. Because gender modified both the relationship between age and cortisol response magnitude and the time course of the response, future studies of HPA reactivity in aging should examine the responses of both males and females.

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