Gender differences in age-related changes in HPA axis reactivity

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Abstract

Possible differences between men and women in age-related patterns of hypothalamic–pituitary–adrenal (HPA) axis response to challenge were examined to test the hypothesis that women show greater age-related increase in HPA axis reactivity to challenge. Twenty-six younger subjects, 9 men and 17 women, ages 22–26 and 14 older subjects, 7 men and 7 women, ages 67–88 participated in the study. Patterns of change in salivary “free” cortisol were measured in response to a standardized, 30-minute cognitive challenge, administered individually to each subject beginning at 1600 h. Consistent with previous research, there was a significant main effect for age with respect to baseline cortisol: older age was associated with higher baseline cortisol ($P<0.001$). Results also provide support for the hypothesized age-by-gender interaction with respect to patterns of response to challenge. There was a significant interaction with respect to maximum percentage increase over baseline ($P<0.002$): among younger adults, the men exhibited greater increases whereas among the older adults, the women exhibited greater increases. A similar, though only marginally significant pattern was seen for total area under the response curve ($P=0.07$). Repeated measures ANOVA confirmed the gender-by-age differences in the patterns of response ($P=0.01$ for time*age*gender interaction). © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Gender differences in morbidity and mortality remain a topic of considerable research interest. Although women enjoy greater longevity (Verbrugge and Wingard, 1987), their relative protection against major causes of morbidity and mortality such as heart disease is greatly reduced post-menopause (Greendale et al., 1999). Though there has been considerable research directed towards understanding the sources of observed gender differences in health and longevity, much remains to be elucidated. Here, we examine the question of possible gender differences in age-related changes in hypothalamic–pituitary–adrenal (HPA) axis reactivity to challenge. Such gender differences are of interest as potential contributors to gender differences in health risks and, in particular, to the known reduction in women’s relative protection against heart disease and stroke post-menopause. Specifically, we examine the hypothesis that women exhibit greater age-related increase in HPA axis reactivity, resulting in greater exposure to elevated levels of cortisol.

Data on patterns of diurnal, plasma cortisol activity suggest an age-related increase in basal cortisol secretion (Deuschle et al., 1997; van Cauter et al., 1996). Significantly, recent analyses comparing age-related changes for men versus women have suggested that women experience larger age-related increases in cortisol secretion, with postmenopausal women exhibiting shorter nocturnal nadirs, higher morning acrophase and higher overall mean 24-hr cortisols (van Cauter et al., 1996). Studies also suggest that women may experience greater age-related increase in HPA axis response to challenge. At younger ages, studies show either greater cortisol response among men (Collins and Frankenhaeuser, 1978; Kirschbaum et al., 1992b) or no significant gender differences (Gallucci et al., 1993; Stoney et al., 1987; Streen et al., 1984). A number of studies of older men and postmenopausal women, however, show intriguing patterns of greater HPA axis reactivity among women in response to CRH challenge (Greenspan et al., 1993; Heuser et al., 1994; Luisi et al., 1998) and a trend towards greater response to physostigmine, a centrally active cholinesterase inhibitor (Peskind et al., 1995). Wilkinson et al. (1997) have also reported that postmenopausal women exhibit less feedback inhibition (i.e., blunted ACTH decline) in response to cortisol infusion, post-metyrapone administration, compared with younger, pre-menopausal women and with older men. Patterns of response to psychological challenge have to date shown a more mixed picture. One study has reported greater ACTH and cortisol response among men in response to a public-speaking challenge (Kudielka et al., 1998). By contrast, we found a pattern of greater ACTH and cortisol in older women as compared with older men in response to a “driving simulation” challenge (Seeman et al., 1995).

Several lines of evidence suggest the possible role of reproductive hormones such as estrogen in this apparent age-related shift towards greater relative HPA axis reactivity among postmenopausal women. First, variations in estrogen have been linked
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