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Review

Sex differences in HPA axis responses to stress: a review

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Contents

1. Overview

In this review article, we set out to update findings on sex differences in hypothalamus–pituitary–adrenal (HPA) axis responses to stress with a main focus on human responses to

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acute psychological stress. First, we briefly describe normal HPA axis regulation under stress exposure as well as HPA axis dysfunction, which manifests in hyper- or hypo-reactivity, and discuss some important methodological issues in the study of acute HPA axis stress responses. We then outline observations of sex-disease dimorphisms that might be related to HPA axis dysfunction. A summary of empirical findings on sex differences in HPA axis stress responses over the life span with respect to laboratory as well as field studies is then provided. Finally, we discuss possible underlying mechanisms explaining at least some of the reported sex differences in the regulation of HPA axis stress responses. These are sexual dimorphisms in brain functioning and the role of circulating sex steroids and corticosteroid binding globulin (CBG).

2. The hypothalamus–pituitary–adrenal axis

The hypothalamus–pituitary–adrenal axis is a central control and regulatory system of the organism that connects the central nervous system (CNS) with the hormonal system. This stress-responsive neuroendocrine system helps the organism adapt to increased demands and maintain homeostasis after challenge but is also vital for supporting normal physiological functioning. The end product, cortisol, has a wide range of physiological effects in the body; virtually all of the body's single nucleated cells are potential targets for cortisol. Cortisol plays a critical role in metabolism by mobilizing resources to provide energy. This helps to overcome the increased metabolic demand presented by a host of challenges. It also regulates or impacts on other important physiological systems, like the immune system, the sympathetic-adrenal-medullary (SAM) axis, the cardiovascular system, as well as affective and cognitive processes.

Under stress, the hypothalamus secretes corticotropin-releasing hormone (CRH), and this provokes the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH triggers the secretion of glucocorticoids from the adrenal cortex. In humans, the main glucocorticoid is cortisol. Cortisol is predominantly (90–95%) bound to binding proteins in blood, only 5–10% of the total plasma cortisol circulates as biologically active, unbound, ''free'' cortisol. Overall functioning is controlled by several negative feedback loops (for an overview, see Dallman et al., 2000; Tsigos and Chrousos, 2002; Watts, 2000).

A dysfunctional HPA axis is associated with manifestations of psychosomatic and psychiatric disorders (for reviews, see Chrousos and Gold, 1992; Heim et al., 2000a,b; Holsboer, 1989; Raison and Miller, 2003; Stratakis and Chrousos, 1995; Tsigos and Chrousos, 1994; Tsigos and Chrousos, 2002; Young, 1998). For example, HPA *hyper*activity is often found in major depression (Björntorp, 1996; Carroll et al., 1976; Gold et al., 1984; Sachar et al., 1970) and also seems to be associated with susceptibility to infectious diseases (Mason, 1991) and cardiovascular problems (McEwen, 1998a). *Hypo*reactivity of the HPA axis system is associated with autoimmune processes such as lupus erythematosis (Weiner, 1991), multiple sclerosis (Adams and Victor, 1989), neurodermatitis (Buske-Kirschbaum et al., 1997; Schnyder, 1960) or fibromyalgia, chronic fatigue syndrome, and rheumatoid arthritis (see Tsigos and Chrousos, 2002). It is generally accepted that exposure to stress can cause and/or intensify numerous diseases. It has been suggested that HPA axis functioning might serve as an indicator of allostatic load, an index

of cumulative toll on the body. A high allostatic load might result from chronic overactivation of the stress system (McEwen, 1998a; McEwen and Stellar, 1993), and result in a number of negative health outcomes in the long run, such as diabetes, hypertension, cancer, and cardiovascular disease (McEwen, 1998a,b).

3. Methodological issues

Since available empirical evidence differs significantly in numerous relevant methodological aspects, it is important to bear in mind a number of study design issues that should influence the evaluation of reviewed data and conclusions that can be reasonably drawn from different studies. Design issues may be classified into the following categories: (1) sample selection/composition and sample size, (2) characteristics of the applied stressor/challenge, (3) the outcome studied, and (4) the implementation of the study protocol.

Concerning sample selection/composition, the most important aspect relates to the 'species' under study. While it is self-evident that primates differ significantly from rodents in multiple aspects (ranging, e.g., from different cortisol to corticosterone ratio, circadian rhythm, or menstrual cycle to cognitive abilities, or self-awareness etc.), animal strains also differ significantly in HPA axis functioning (for example, Fischer 344 rats versus Lewis/N rats, or BALB/c mice versus C57/BL mice). In humans, the sample composition in relation to health status as well as age at testing is an important consideration. Furthermore, the number of subjects is an important criterion due to its influence on statistical power and the ability to detect sex effects in a given study sample.

Another important design aspect is the type of stressor/challenge (e.g., psychological stress, physical exercise, pharmacological stimulation; real-life stressor versus laboratory setting) as well as the duration of stress exposure (acute versus chronic). While psychological stressors are central stimuli, pharmacological challenges act at different levels of the HPA system and function in a dose-dependant manner (e.g., testing a system component's maximal capacity or sensitivity; see also below). Laboratory stress protocols offer the advantage of standardization across test sessions but might lack the ecological validity of field studies or ambulatory assessments. Importantly, however, the variety of stress tasks most commonly employed in the laboratory have different potencies in their ability to reliably evoke HPA axis responses (see Biondi and Picardi, 1999). In an excellent recent meta-analysis of 208 laboratory stress studies, Dickerson and Kemeny (2004) investigated conditions capable of eliciting HPA axis stress responses. They found that motivated performance tasks elicited cortisol responses, controlling for methodological factors and other stressor characteristics, if they were uncontrollable or characterized by social-evaluative threat. Tasks containing both elements were associated with the largest cortisol and ACTH changes and the longest recovery time. The Trier Social Stress Test (TSST) is a highly standardized laboratory stress task consisting of a preparation period (3 min), a free speech (5 min), and mental arithmetic task (5 min) in front of an audience, which is characterized by both uncontrollable and social-evaluative elements. We could repeatedly achieve responder rates of >70% applying the TSST (Kirschbaum et al., 1993; Schommer et al., 2004).

While in blood both bound and free cortisol can be measured, only free cortisol appears in saliva. Cortisol levels measured in saliva agree very well with the amount of free cortisol in blood (absolute levels of free cortisol are lower in saliva due to a relative abundance of the cortisol-metabolizing enzyme 11-beta-HSD), but show only moderate correlations with total cortisol levels under certain circumstances (see below). Hence, collection of salivary cortisol provides a noninvasive (i.e., no stress of venipuncture) and relatively inexpensive means to obtain an index of the biologically active fraction of this steroid hormone. More detailed information on sampling, storage and biochemical analysis are provided elsewhere (see Kirschbaum and Hellhammer, 1989, 1994, 2000).

Several samples should be collected over the course of a stress session to cover basal HPA axis functioning, the initial response phase, and the recovery phase. Initial free salivary cortisol responses can be observed 5–20 min after stress with peak levels 10–30 min after cessation of the stressor. Basal levels are typically regained after 60–90 min. As recently reported by Kudielka et al. (2004a), psychological stressors, in contrast to pharmacological challenge tests, can be applied with equal reliability in the morning as well as afternoon hours. It is important to note also that prolonged periods of stress can lead to a cortisol secretion that is sustained over several hours.

Finally, it has to be considered that there are several sources of inter-individual differences in HPA axis stress responses in humans which should, if possible, be held constant or controlled (e.g., health status, smoking habits, female menstrual cycle phase, personality factors, time of day, habituation effects due to repeated stress exposure, social support, genetic factors, etc.; for detailed review, see Kirschbaum and Hellhammer, 1994; Kirschbaum et al., 1998).

4. Sex-disease dimorphisms

In humans, sex-disease dimorphisms can be observed. Men and women are at differential risks for a number of illnesses. This observation is reflected by sex-specific prevalence rates for several diseases with women suffering more often from autoimmune illnesses, whereas men are more prone to develop coronary heart diseases or infectious diseases (McCarty et al., 1995; see also Kudielka et al., 2000a,b). Concerning psychiatric disorders, women more often develop anxiety, depression, phobia, or panic disorders, whereas men more often show antisocial behavior or substance abuse (Bebbington, 1996; Cleary, 1987; Weich et al., 2001). Interestingly, several studies ranging from everyday hassles to post-traumatic stress reactions conclude that women subjectively experience more stress than men and consistently report more physical as well as somatoform symptoms and show higher stress vulnerability (Bebbington, 1996; Kessler et al., 1981; Kessler and McLeod, 1984; Kroenke and Spitzer, 1998; Miller and Kirsch, 1987; Troisi, 2001). In contrast, life expectancy for females is about 7 years longer than that for men. It may be speculated that differences in health status may at least in part be related to sex differences in stress responsivity. If this is the case, it may be that sex-specific stress responses reflect causal links and are not merely epiphenomena of sex-specific prevalence rates of several disorders.

For decades investigators have asked whether males and females differ in stress-related HPA axis responses. Interestingly, several studies have shown that HPA axis stress responses appear not to parallel or reflect the subjective response to psychological or noxious stress (Buske-Kirschbaum et al., 2003; Frankenhaeuser et al., 1976; Kirschbaum et al., 1999, 1996; Kudielka et al., 1998; Zimmer et al., 2003). Therefore, it cannot be easily extrapolated from emotional or verbal reports of perceived stressfulness to a physiological response of the organism to a stressful encounter.

5. Sex differences in HPA axis stress responses

At first glance, the overall resulting picture might appear inconsistent or even contradictory. However, it has to be considered that studies providing the available empirical evidence have differed significantly in numerous important methodological aspects (as outlined above). In the following, we review empirical evidence with a main focus on sex differences in stress-related HPA axis responses to psychological stressors in humans.

Over the years, a relatively consistent picture has emerged regarding sex differences in animal data. Numerous studies have shown that glucocorticoid levels are higher in females than in males after HPA axis stimulation (Haleem et al., 1988; Heinsbroek et al., 1991; Kant et al., 1983; Kitay, 1961, 1963; Yoshimura et al., 2003). In contrast, empirical evidence is much more equivocal in humans. While HPA axis responses to physical exercise appear not to differ between men and women (Friedmann and Kindermann, 1989; Kirschbaum et al., 1992a; Kraemer et al., 1989), most psychological stress studies revealed that there are (a) no significant sex differences or (b) higher cortisol responses in young men than in young women after exposure to acute real-life psychological stress (e.g., academic exams) or controlled laboratory stress tasks (e.g., free speech, mental arithmetic, harassment; Collins and Frankenhaeuser, 1978; Earle et al., 1999; Forsman and Lundberg, 1982; Frankenhaeuser et al., 1980, 1978; Kirschbaum et al., 1995a,b; Lundberg, 1983; Nicolson et al., 1997; Polefrone and Manuck, 1987; Stoney et al., 1987; Stroud et al., 2002). Interestingly, ACTH and free cortisol increases in men were up to twice as high as in women and the sole anticipation of an upcoming psychosocial stress task led to a significant free cortisol response in men only (Kirschbaum et al., 1992b). In subjects with higher compared to lower chronic stress levels, Matthews et al. (2001) observed lower plasma cortisol levels during recovery from acute stress. These data were interpreted as indicating HPA axis suppression; the authors did not report on sex differences in either cortisol reactivity or recovery. In a recent study of 81 healthy young adults, we applied the Trier Social Stress Test in men, women in the follicular phase of the menstrual cycle, women in the luteal phase, and women using oral contraceptives (OC). The results disclosed that significant sex differences emerge for ACTH and free salivary cortisol but not for total plasma cortisol stress responses (Kirschbaum et al., 1999). The study showed that ACTH responses are elevated in men compared to women, regardless of menstrual cycle phase or use of oral contraceptives. Women in the luteal phase had comparable saliva cortisol stress responses to men whereas women in the follicular phase or women taking oral contraceptives showed significantly lower free cortisol responses. These observations

point out the necessity of strictly distinguishing between the total cortisol secretion and the levels of bioavailable free cortisol (see Fig. 1).

The same sex effect emerged for elderly subjects with men evincing higher ACTH, free salivary cortisol (Kudielka et al., 1998) or total plasma cortisol (Traustadottir et al., 2003) than women. Traustadottir et al. (2003) applied the Matt Stress Reactivity Protocol (MSRP), composed of the Stoop color word task, a mental arithmetic test, an anagram test, the cold pressure test, and an interpersonal stressor in their study. In contrast, Seeman et al. (1995) reported on higher plasma cortisol reactivity in elderly women compared to elderly men employing a driving simulation challenge. Recently, these observations were corroborated by the same group using a 30-min cognitive challenge paradigm (Seeman et al., 2001). However, a closer look at the results of these two studies reveals that in the first study (Seeman et al., 1995) no significant sex effects were observed in mean plasma cortisol responses in terms of (a) maximal increase, (b) area under the curve, and (c) repeated measures ANOVA, but solely in simultaneously elevated ACTH- and cortisol responses above the respective sample median. In the second study (Seeman et al., 2001), the reported effect of elevated saliva cortisol responses in older women compared to older men as well as younger men and younger women were based on only two subjects in the group of elderly female responders (non-responders were excluded by the authors). For a recent meta-analysis of cortisol responses to pharmacological and psychological challenge tests in human aging (see Otte et al., 2005).

In children, controlled stress studies are extremely rare. The few data available, including responses to psychosocial laboratory stress, adjustment to a (new) day-care situation, and surgical stress seem to point towards similar stress-related cortisol responses in younger and older children with no apparent sex differences (Buske-Kirschbaum et al., 1997, 2003; Khilnani et al., 1993; Lundberg, 1983; Tout et al., 1998). However, a study of stress responses in 18 male and 18 female newborns suggests that sex differences in adrenocortical responses might be present at birth (Davis and Emory, 1995). The mildly stressful behavioral assessment procedure, the Neonatal Behavior Assessment Scale (NBAS; Brazelton, 1973) revealed higher free cortisol responses in male neonates. Dahl et al. (1992) applied a pharmacological stimulation via exogenous CRH administration in 25 healthy children (mean age 10.3 ± 1.6 years) and found a significantly higher total plasma cortisol peak in boys than in girls. Further studies in this field are needed to draw final conclusions.

In the past, most studies focused separately on the effects of age (for an excellent review, see Seeman and Robbins, 1994) or sex and to the best of our knowledge there are no data sets available on sex differences in stress-induced HPA axis responses in multiple age groups ranging from children to elderly adults. Therefore, we recently set out to perform a reanalysis of five independent studies from our laboratory in which subjects were confronted with the TSST protocol at the same time of day (Buske-Kirschbaum et al., 1997, 2003; Kirschbaum et al., 1999; Kudielka et al., 1999, 2000b). In this data set, we only included those subjects who were healthy (patient groups were excluded) and received only placebo treatment. Postmenopausal women were free of any hormonal replacement therapy (HRT) and in case of pre-menopausal women only participants in the luteal phase were selected. In sum, this analysis was based on 102 healthy subjects between 9 and 76 years (Kudielka et al., 2004b). Results showed that the stress task induced significant HPA

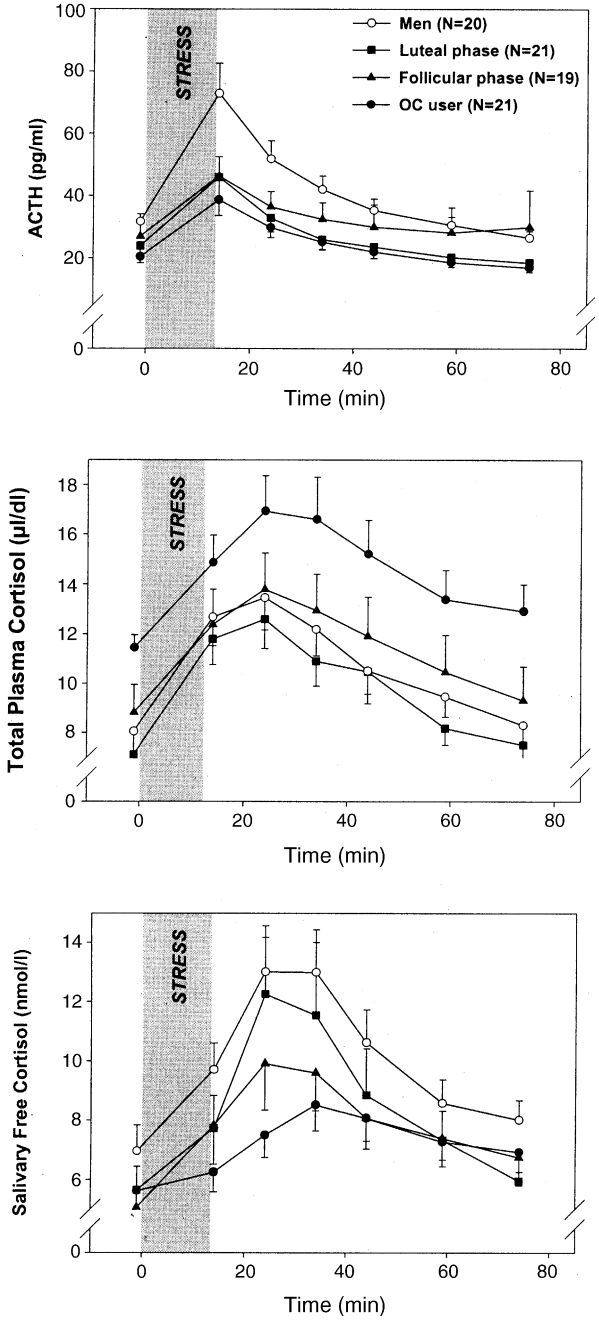

Fig. 1. Mean (±S.E.M.) ACTH (pg/ml), total plasma cortisol (μg/dl) (conversion of cortisol: μg/dl × 27.6 = nmol/l), and free salivary cortisol (nmol/l) responses in men, women in the luteal phase, women in the follicular phase, and women using oral contraceptives (OC) before and after stress (TSST). The *shaded area* indicates the period of stress exposure (data taken from Kirschbaum et al., 1999).

axis responses in all age groups in both males and females (see Fig. 2). The data revealed no sex differences in free cortisol responses in children and younger adults, but larger free cortisol responses in elderly men than in elderly women. This effect did not appear to be attributable to subjective responses to the TSST. For total plasma cortisol, the response patterns did not differ between age and sex groups. However, total plasma cortisol concentrations were generally heightened in elderly women. For ACTH, the response was higher in younger adults, primarily due to an elevated response in younger men. The observed ACTH and total plasma cortisol response patterns in younger and older adults suggest that a heightened hypothalamic drive in younger men decreases with age, resulting in similar ACTH responses in elderly men and women and that younger adult females have a higher adrenocortical sensitivity to ACTH signals. This is in accordance with earlier findings from Horrocks et al. (1990) who reported on greater ACTH pulses in middle-aged men and Roelfsema et al. (1993) who found a higher sensitivity to ACTH of the female adrenal cortex.

Nevertheless, the possibility that different stress protocols cause stressor-specific HPA axis responses can not yet be ruled out. In a series of impressive studies, Kiecolt-Glaser and coworkers investigated the influence of marital conflict on immunological parameters and also reported some neuroendocrine findings. In one study, ACTH and plasma cortisol levels were monitored during a 24-h period in newlywed couples for whom the day included a conflict. It was concluded that women (wives) demonstrate greater and more persistent physiological changes to marital conflict than men (husbands; Kiecolt-Glaser et al., 1998, 1996). Unfortunately, absolute hormone levels cannot be abstracted from the reported regression analyses. In another study, the absence of significant sex differences in hormonal responses was reported (Kiecolt-Glaser et al., 1997). In this sample of older couples participating in a 30-min conflict discussion and a 15-min recovery session, a significant slope (rate of linear change over time) could only be observed in the ACTH response in females. Another recent report points to the possibility of the importance of the gender relevance of psychological stressors. Stroud et al. (2002) reported on higher free cortisol stress responses in women compared to men after two social interaction challenges (social rejection), based on the Yale Interpersonal Stressor (YIPS) (Stroud et al., 2000). In this study, 50 healthy volunteers (24 men and 26 women) were randomly assigned to an achievement or a rejection stress condition. It was hypothesized that situations involving intellectual inferiority and performance failures were perceived as more stressful by men and that the male stress responses may predominantly involve the traditional ‘‘fight and flight’’ reaction while women’s stress response may be better characterized by ‘‘tend and befriend’’, involving nurturant activities and the creation of social networks (see also Bebbington, 1996; Klein and Corwin, 2002; Taylor et al., 2000). The data showed that men but not women had significant free cortisol increases after confrontation with the achievement challenges (mathematical and verbal tasks) whereas women but not men showed significant free cortisol responses to the social rejection challenges. The observed sex differences in salivary cortisol cannot be caused by a high number of women on birth control pills in the academic achievement condition because women taking oral contraceptives were not eligible in this study and the relative number of women in the luteal versus follicular phase did not differ significantly between conditions. Although the observed stress-related increases reached significance, net increases appeared to be small

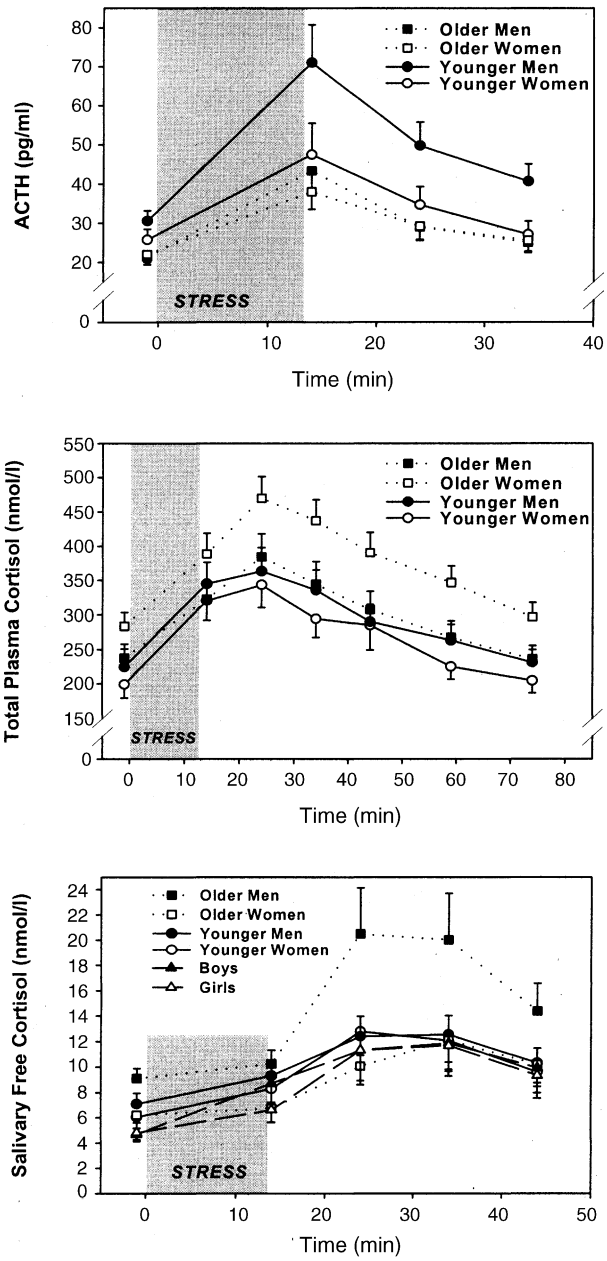

Fig. 2. Mean (±S.E.M.) ACTH (pg/ml) and total plasma cortisol (nmol/l) responses in elderly and younger men and women, and free salivary cortisol (nmol/l) in elderly and younger men and women as well as boys and girls before and after stress (TSST). The *shaded area* indicates the period of stress exposure (data taken from Kudielka et al., 2004b).

and the depicted standard errors (S.E.M.) were relatively high. Therefore, further studies using different standardized and validated stress protocols are warranted.

Whether the factors that account for variability within each sex group may be different even when group differences in stress responses are absent or small is another important issue. For example, perceived challenge or threat may predict responses among men, while interpersonal concerns may be more important among women. However, in the meta-analysis of Dickerson and Kemeny (2004) the importance of the two task elements, namely uncontrollability and social evaluative-threat, to elicit HPA axis stress responses was not significantly modified by the sex of study participants. Specifically, effect sizes could not be significantly predicted by sex, suggesting that sex did not explain the variability of observed cortisol and ACTH responses between study protocols.

It is also possible that sex differences in HPA axis responses to psychological stress might be different within clinical populations than in healthy volunteers. Data from Peeters et al. (2003) recently provided some evidence that salivary cortisol responses to negative daily events were larger in female patients suffering from major depressive disorders (MDD) than in male patients. However, in a laboratory-based study employing the TSST, Young et al. (2004) compared male and female patients with depression and/or anxiety disorders with healthy controls, and found no gender or diagnosis-related effects for plasma cortisol (but an exaggerated ACTH response in the depressed group with comorbid anxiety disorder). Though all male subjects had higher baseline and post-challenge ACTH levels (mean ACTH increase = 5.1 pmol/l) compared with all female subjects (mean ACTH increase = 2.6 pmol/l). Thus, Young et al. (2004) found that both patients and normal control subjects demonstrated similar sex differences for ACTH and no sex difference in plasma cortisol measures. Condren et al. (2002) did not find any significant correlations between increases in plasma cortisol and sex for patients with social phobia and healthy controls. Although other laboratory studies investigated HPA axis stress responses to acute psychological stress in clinical populations, they did not analyze sex differences (Furlan et al., 2001; Levin et al., 1993; Young et al., 2000) or only studied males or females (Gerra et al., 2000; Heim et al., 1998, 2001; Martel et al., 1999).

In terms of pain-related stress responses, a study by Petrie et al. (1999) measured endocrine effects after lumbar puncture and reported higher and more prolonged HPA axis responsiveness in elderly females. It should be taken into consideration, however, that this analysis was based on a sample of only five male and four female healthy controls and only seven male and three female patients with Alzheimer's disease. In contrast, a recently conducted study by Zimmer et al. (2003) investigated sex differences in salivary cortisol responses to noxious stress in a laboratory setting (modified cold pressure test: plunge test) in 76 healthy young adults (39 males and 37 females). They reported a small but significantly larger free cortisol increase in men than in women, an effect that could neither be attributed to sex differences in cortisol levels at baseline, tolerance time nor ratings of pain intensity and unpleasantness. It is possible, however, that the observed sex effect could be attributed to the impact of birth control pills since 25 women were on OC control, while 9 participated during the follicular, and 8 during the luteal phase. Pharmacological tests, including the application of different doses of physostigmine, CRH, metyrapone plus exogenous glucocorticoids, or high intensity exercise after a high dose of dexamethasone pretreatment resulted in (a) no significant sex differences or (b) significantly or slightly

elevated HPA axis responses and decreased feedback sensitivity in female participants, an effect which seems to be more pronounced with increasing age (Born et al., 1995; Deuster et al., 1998; Gallucci et al., 1993; Greenspan et al., 1993; Hermus et al., 1984; Heuser et al., 1994; Kirschbaum et al., 1992a; Luisi et al., 1998; Otte et al., 2005; Wilkinson et al., 1997; Young et al., 1990).

The observation that acute psychological stressors on one hand (like the TSST or real-life college exams) and pharmacological stimulation tests on the other (like CRH-injections) seem to result in different sex-specific patterns of HPA axis responsivity points to the necessity of clarifying exactly what the applied tests measure and which levels of the HPA axis are activated. Depending on the nature of a stimulus, different pathways of the HPA axis are activated. Psychological stressors activate the HPA axis by stimulation of the paraventricular nucleus (PVN) of the hypothalamus through the limbic system (prefrontal cortex, hippocampus, amygdala), whereas physiological stressors have a more direct pathway to the PVN (Herman and Cullinan, 1997). While most HPA axis stimulation tests primarily act at the pituitary or adrenal level, psychological stressors certainly require processing at higher brain levels. It is also necessary to consider the possibility that different doses of a pharmacological trigger change the focus of the chosen test. For example, when assessing adrenal cortex functioning, administration of a small dose of synthetic ACTH (e.g., 1 μg) would test for HPA axis sensitivity, while administration of a larger dose of synthetic ACTH (e.g., 250 μg) would assess its maximum capacity. Consequently, reported sex differences could possibly be attributed to differences in the applied HPA axis stimulation procedures.

Finally, besides stress-related cortisol increases, time to recovery seems to be an important index and therefore, more fine-grained analyses of recovery should be provided in future stress studies. In their informative review on aging and HPA axis response to challenge in humans, Seeman and Robbins (1994) underscore this idea by defining the term stress resilience as ‘‘the overall pattern of HPA responses to challenge, encompassing the rate of initial response to challenge, the magnitude of the response, and the rate of recovery of the HPA axis to the basal state’’. It can be hypothesized that beside absolute peak levels, patterns of recovery after stress exposure might also be relevant for health outcomes (Dienstbier, 1989; Linden et al., 1997), and that there is a heightened risk for a negative health outcome when recovery is prolonged or prevented (Sapolsky et al., 2000). This issue is also discussed in the allostatic load framework (McEwen, 1998a,b). Indeed, a quick, strong HPA axis response coupled with a rapid recovery process could be adaptive, first providing the organism with the necessary energy to cope with an enfaced challenge followed by an adequate return to baseline conditions (Linden et al., 1997; Sapolsky et al., 2000). A sluggish return to the basal state could result in longer overall exposure to stress hormones and could indicate an underlying dysfunction of the stress system (Sapolsky et al., 2000).

6. Sexual dimorphisms in brain functioning, circulating sex steroids, and corticosteroid binding globulin

Observed sex differences in HPA axis stress responses may be due to sexual dimorphisms in brain function and circulating sex steroid and corticosteroid binding

globulin levels. Brain limbic regions, including the prefrontal cortex, the hippocampus, and amygdala, are presumed to be involved in the processing of psychological stress (Herman and Cullinan, 1997; Herman et al., 1996). There is evidence indicating that neurobiological mechanisms and hippocampal structures underlying higher-order cognitive processing are sexually dimorphic (Herman and Cullinan, 1997; Shors et al., 2001; for overview, see also Wizemann and Pardue, 2001). Brain imaging studies (e.g., PET scans, fMRI) have observed sex differences in the lateralisation of the activation in the amygdala in response to emotionally arousing film clips (Cahill et al., 2001; Killgore and Yurgelun-Todd, 2001).

Other prime candidates for explaining sex differences in HPA stress responsiveness are circulating gonadal steroids. Among them, estradiol especially seems to exert modulating effects on HPA axis functioning, including HPA axis responsiveness and sensitivity to glucocorticoid negative feedback (Young, 1995a,b). Animal studies consistently reveal a strong stimulatory influence of estradiol on HPA axis functioning (Handa and McGivern, 1999; Kitay, 1961, 1963; Lesniewska et al., 1990; Norman et al., 1992; Viau and Meaney, 1991; Xiao et al., 1994) with modulatory effects on mineralocorticoid and glucocorticoid receptors (Burgess and Handa, 1992; Carey et al., 1995; Peiffer et al., 1991; Redei et al., 1994; Turner, 1992). Moreover, estradiol may directly enhance CRH gene transcription in the hypothalamus through binding to estrogen-responsive elements on the CRH gene (Vamvakopoulos and Chrousos, 1993). Whereas many animal studies can be cited that have directly investigated the impact of estrogens on HPA axis regulation, few experimental studies have been conducted in humans and the empirical evidence is rather inconsistent. For example, in young men, a 48-h estradiol-application resulted in elevated free cortisol responsivity (Kirschbaum et al., 1996), whereas a two-week estradiol treatment in postmenopausal women did not alter TSST-induced HPA axis responses. However, feedback sensitivity as measured by the combined dexamethasone-CRH-test seemed to be increased in postmenopausal women after the two-week estradiol substitution (Kudielka et al., 1999). Lindheim et al. (1992) reported that postmenopausal women showed a stress-induced HPA axis response before estradiol treatment but not after a six-week sex hormone replacement, although it can be speculated that this effect is merely based on habituation effects to the repeatedly applied stress procedure. Del Rio et al. (1998) could not show any estradiol effects on HPA axis responsivity in a cross-over design, applying a relatively mild stressor. From other studies, no clear conclusions can be drawn due to small sample sizes and methodological problems (Collins et al., 1982; Liu et al., 1987).

Androgens exert specific and in part contrasting effects at different levels of HPA axis regulation as shown in several animal studies (Bingaman et al., 1994; El Hani et al., 1980; Handa et al., 1994; Kitay, 1963; Lesniewska et al., 1990; Viau and Meaney, 1996), but it should be noted that testosterone can also exert estrogenic effects after being metabolized to estrogen by aromatization in both brain and peripheral tissues (Bagatell et al., 1994; Chowen et al., 1990; Finkelstein et al., 1991; Naftolin, 1994; Weissberger and Ho, 1993). Experimental human data are extremely rare. In a placebo-controlled double blind study, we investigated HPA axis stress responses to the TSST in 75 men and women of advanced age after a two-week dehydroepiandrosterone (DHEA) or placebo treatment (Kudielka et al., 1998). Women treated with DHEA showed ACTH stress responses similar to those of

men but significantly enhanced compared to women taking placebos. No other stress response differences emerged between DHEA and placebo groups.

Finally, although estradiol-mediated effects seem to be the most potent modulators of HPA axis stress regulation, progesterone might also contribute. In animal studies, it was shown that progesterone can function as a glucocorticoid antagonist, can bind to glucocorticoid and mineralocorticoid receptors (at a different site than glucocorticoids), can increase the rate of dissociation of glucocorticoids from the receptor, can modulate the receptor number in the hippocampus, and can diminish the effectiveness of cortisol feedback on stress responsiveness (Ahima et al., 1992; Carey et al., 1995; Duncan and Duncan, 1979; Keller-Wood et al., 1988; Rousseau et al., 1972; Svec, 1988; Turner and Weaver, 1985). However, data on the impact of progestins on the HPA axis in humans are extremely sparse and available results do not suggest a significant mediation of ACTH and cortisol stress responses (Burleson et al., 1998; Lindheim et al., 1994).

Beside the role of sex steroids, it is also possible that some of the observed differences in HPA axis reactivity could be explained by different CBG levels in males and females. In our reanalysis of five different laboratory stress studies described above (Kudielka et al., 2004b), CBG levels were available for younger and older adults. Compared to older men, CBG levels were significantly higher in older women, though no sex differences emerged in younger adults. The elevated total plasma cortisol levels in older women and possibly, at least in part, the higher free salivary free cortisol responses in older men may be attributable to the observed differences in CBG levels.

In sum, the overall picture seems to indicate that adult men respond to psychological stress with greater increases in cortisol compared to women. It can be hypothesized that on one hand the greater stress reactivity observed in men might be causally associated with an elevated risk for diseases associated with high levels of cortisol such as cardiovascular disease and diabetes and may help explain the higher prevalence for these diseases in males. On the other hand, the lower cortisol response observed in women may be related to a hyporeactivity of the HPA axis, which is associated with an increased risk for autoimmune diseases, a condition much more prevalent in women. Much more research is warranted on the importance of stressor specificity. Based on only a few studies applying interpersonal or psychosocial conflict tasks in contrast to the more usual ‘‘academic’’ achievement stressors, the hypothesis that women show higher responses in interpersonal tasks remains speculative. However, it was reasoned that higher rates of depression and anxiety disorders in women might reflect hyperactive stress responses in interpersonal settings in females. Finally, sex differences in the structure of limbic regions of the brain and the cognitive processing of a stressor as well as differences in circulating sex steroids and CBG levels may be responsible for the described sexually dimorphic HPA axis stress responses.

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