



REVIEW

# The effects of sex and hormonal status on the physiological response to acute psychosocial stress

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**Summary** Whether one is male or female is one of the most important determinants of human health. While males are more susceptible to cardiovascular and infectious disease, they are outnumbered by women for many autoimmune disorders, fibromyalgia and chronic pain. Recently, individual differences in the physiological response to stress have emerged as a potentially important risk factor for these disorders. This raises the possibility that sex differences in prevalence of disease could at least in part be explained by sex differences in the nature of the physiological response to stress.

In a psychophysiological laboratory, the autonomic nervous system response can be provoked by many different stressors including physical, mental and psychosocial tasks, while the hypothalamic-pituitary-adrenal axis (HPAA) response seems to be more specific to a psychosocial challenge incorporating ego involvement. The responses of both systems to different psychosocial challenges have been subject to extensive research, although in respect of sex differences the HPAA response has probably been more systematically studied. In this review, we focus on sex differences in HPAA and autonomic nervous system responses to acute psychosocial stress. Although some differences are dependent on the stressor used, the responses of both systems show marked and consistent differences according to sex, with the phase of the menstrual cycle, menopausal status and pregnancy having marked effects. Between puberty and menopause, adult women usually show lower HPAA and autonomic responses than men of same age. However, the HPAA response is higher in the luteal phase, when for example poststress free cortisol levels approach those of men. After menopause, there is an increase in sympathoadrenal responsiveness,

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which is attenuated during oral hormone replacement therapy, with most evidence suggesting that HPAA activity shows the same trends. Interestingly, pregnancy is associated with an attenuated response of the sympathoadrenal and HPAA systems at least as assessed by biochemical stimulation.

It is likely that these sex differences in autonomic function are a result of estrogen exposure which attenuates sympathoadrenal responsiveness. The HPAA is however somewhat more complex and evidence now suggests the influence of other modifiers such as arginine vasopressin (AVP) and the regulation of circulating cortisol bioavailability by corticosteroid-binding globulin (CBG).

The pronounced and multi-faceted sex differences in stress responsiveness suggest that they are a product of a strong evolutionary pressure. We hypothesise that this has to a great deal been driven by the need to protect the fetus from the adverse effects of maternal stress responses, in particular excess glucocorticoid exposure. Studying this hypothesis may have a fundamental impact on our understanding about how adult health is set during early life and how adult disease could be prevented in men and women.

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## 1. Introduction

Being male or female is one of the most important predictors of an individual's health. Compared with women of similar age, men have a higher risk of arteriosclerosis (Kalin and Zumoff, 1990) and infectious disease (Klein, 2000), while women outnumber men for several autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis (Beeson, 1994; Whitcare et al., 1999), as well as many stress-related bodily complaints such as fibromyalgia (Wolfe et al., 1995) and chronic pain (Verhaak et al., 1998). Knowing what biological mechanisms underlie such profound differences may be extremely helpful in elucidating the pathogenesis of various common disorders, a step crucial in developing their prevention and treatment. However, despite recent progress, the mechanisms behind these sex differences remain insufficiently understood.

Individuals react to stressful events in different ways, and differences in *the* physiological stress response are important determinants of health. A stressful stimulus results in the activation of several physiological pathways including the hypothalamic-pituitary-adrenal axis (HPAA) and the autonomic nervous system. A considerable body of research during recent years has linked the function of both of these systems with the pathogenesis of several common disorders including coronary heart disease, type 2 diabetes, the metabolic syndrome, depression and stress-related bodily complaints (Stoney et al., 1990; Schobel et al., 1996; Phillips et al., 1998, 2000; Heim et al., 2000; Yang et al., 2000; Kajantie et al., 2002, 2003a; Tsigos and Chrousos, 2002; Treiber et al., 2003; Kreier et al., 2003; Schwartz et al., 2003;

Brown et al., 2004). Importantly, both systems show a clear sex-specific pattern of response. Therefore, stress reactivity is a major candidate for a mechanism explaining why some diseases are more common in males and others in females.

Some recent reviews have been published related to sex-differences in stress responsiveness. Based on their long-term programmatic work in the field, Kudielka and Kirschbaum (2005) review sex differences in HPAA responsiveness providing in particular a thorough discussion on methodological issues. Otte et al. (2005) have performed a meta-analysis of studies on the effect of age and sex on HPAA response to physiological, pharmacological or psychosocial challenge. In contrast, the objective of our review is to provide a systematic and comprehensive description of human studies assessing how sex and hormonal status affect HPAA and autonomic nervous system responsiveness to acute psychological stressors. This has led the development of the hypothesis that the origin of these sex differences arises from the need to protect the developing fetus from excessive exposure to stress hormones in utero. To elucidate potential mechanisms of these relationships, we refer to selected human studies using other stimulators of these systems as well as a number of elegant animal models important in understanding the overall framework; however, a comprehensive evaluation of these studies remains outside the scope of this review.

## 2. Measuring the stress response

The assessment of stress responsiveness requires a reproducible stressor that is severe enough to

produce a detectable response but moderate enough to reveal differences between individuals. This prerequisite is easier to fulfil in a laboratory setting rather than in normal living conditions. However, to be meaningful a laboratory stressor should bear some resemblance to stressful events in everyday life. Two types of stressors are commonly used: psychosocial tasks such as public speaking, carrying out mathematics or other tasks performed during time pressure, and physiological tests such as the cold pressor test, administration of a protein-rich lunch or exercise testing. Although the focus of this review is on responses to psychosocial stressors, we shall briefly summarize the most common physiological challenges used. It is important to note that exposure to different types of stressors may result in different physiological responses, for example some may be characterised by intense HPAA stimulation while the effect of others may be confined to the autonomic nervous system.

Of the various psychosocial stressors, the physiological response to public speaking has possibly been most extensively studied. The most consistent HPAA stimulation appears to be produced by the The Trier Social Stress Test (TSST; Kirschbaum et al., 1993), in which the subject stands in front of a two- or three-person audience and a video recorder and gives a 5-min talk about his/her personal capabilities, which is followed by a mental arithmetic task. In a recent comprehensive review (Dickerson and Kemeny, 2004), the maximization of HPAA activation was considered to require a rather specific setting with ego involvement and social-evaluative judgement by others acting as key elements. In that review, the TSST was considered superior to other stressors in producing an HPAA response. In addition, the TSST stimulates the sympathetic nervous system, as assessed by heart rate, blood pressure and plasma catecholamine concentrations (Kirschbaum et al., 1996a; Kudielka et al., 1998; Heinrichs et al., 2001). By contrast, mental arithmetic tasks alone such as serial subtractions stimulate the sympathetic nervous system but often not the HPAA (Earle et al., 1999). However, HPAA activation becomes apparent if the arithmetic task is combined with annoyance, for example, in the form of repetitive noise (Komesaroff et al., 1999, 2002) or harassing comments by an investigator (Earle et al., 1999). Other mental tasks such as combining a written name of a colour with another word written in that colour ('Stroop test') or tracing an outline of a figure while looking only at its reverse image in a mirror ('mirror drawing') are thought to produce a predominantly sympathoadrenal stimulation although the HPAA response to these tests alone has been rarely studied.

Some real-life situations are considered reproducible enough to serve as standard stressors. A stressful examination gives rise to both HPAA and sympathoadrenal stimulation (Frankenhaeuser et al., 1978). The HPAA response to awakening is relatively robust and reproducible (Pruessner et al., 1997; Wüst et al., 2000a), interestingly shows a heritability of 40% (Wüst et al., 2000b) and correlates closely with ACTH-stimulated plasma total cortisol (Schmidt-Reinwald et al., 1999), although in elderly women this correlation appears to be weaker (Kajantie et al., 2004). It is of note that the awakening response, while higher in early awakeners (Kudielka and Kirschbaum, 2003; Federenko et al., 2004), was found to be independent of sex and menstrual phase in a study of 52 healthy males and 12 women in the follicular and 11 in the luteal phase (Kudielka and Kirschbaum, 2003). Some testing scenarios, such as a couple attending a marital conflict-stimulating task together (Malarkey et al., 1994), have attempted to combine the realism of a real-life situation with the monitoring possibilities of a laboratory. It may also be argued that a fasting plasma total cortisol measurement, which is obtained by venipuncture usually when a subject attends an unfamiliar clinic after an overnight fast, may in fact be a form of a stress test. However, interindividual differences in real-life settings are likely to be considerable larger than those obtained in a laboratory.

Apart from purely psychosocial stressors, specific physiological stimuli have been used to assess individual differences in the stress response. These include HPAA stimulation by a meal, in particular one rich in protein (Slag et al., 1981; Anderson et al., 1987; Gibson et al., 1999), or by single amino acids such as 5-L-hydroxytryptophan or L-tyrosine (Ishizuka et al., 1983; Schruers et al., 2002), which in addition stimulates catecholamine release (Rasmussen et al., 1983). Glucose or fat alone do not cause detectable HPAA stimulation. However, when interpreting studies on psychosocial stress it is important to note that when a nutrient load is followed by psychosocial stress, the effects are reversed: preceding glucose load amplifies greatly the effects of TSST on salivary cortisol, with no similar effect seen after protein or fat load (Kirschbaum et al., 1997; Gonzales Bono et al., 2002). Other commonly used stimulators are cold pressor tests and exercise, which is thought to increase AVP secretion by the supraoptic and paraventricular nuclei of the hypothalamus (Deuster et al., 1998) which then act to potentiate CRH action at the level of the pituitary ACTH-secreting corticotrophs. A recently described HPAA stimulator is exposure to high concentrations of

inhaled CO<sub>2</sub>, which has traditionally been used to provoke panic disorders. Although the mechanisms remain unknown, a single breath of 35% CO<sub>2</sub> has been found to provide a fast and apparently safe way to stimulate the HPAA (Argyropoulos et al., 2002).

### 3. Sex differences in stress responsiveness

In a 1987 meta-analysis of 12 psychophysiological studies examining the relationship between sex and stress responsiveness, Stoney et al. concluded that there was only limited support for sex differences in response (Stoney et al., 1987). Whereas women had lower systolic blood pressure responses, the urinary catecholamine data were equivocal and the glucocorticoid responses did not differ. One of the major criticisms of these early studies was that the psychological stressors employed, while sufficient to study autonomic nervous system reactivity, were not severe enough to stimulate an HPAA response. Over the past decade, however, the situation has become much clearer as a result of the development of psychological tests able to generate adequate HPAA responses, for example the Trier Social Stress Test (Kirschbaum et al., 1993; reviewed by Dickerson and Kemeny, 2004; Kudielka and Kirschbaum, 2005). The conclusion of these studies, summarised in Table 1, is that sex differences in the basal, unstressed state are subtle but become greatly pronounced following a psychological stressor. Although there are exceptions, in general between puberty and menopause, HPAA and autonomic responses tend to be lower in women compared to men of same age. However, before puberty and after menopause, the sex differences are either smaller or non-existent. For example, in a study of 20 men and 61 women exposed to the TSST, Kirschbaum et al. (1999) showed that ACTH responses in women were lower and accompanied by smaller rises in salivary free cortisol concentrations. These findings were also observed in a study of 39 men and 36 women (Kudielka et al., 1998); women had lower ACTH, total and free cortisol responses. Although not seen in all studies, findings on cardiovascular and sympathoadrenal responses have been characterised by increased blood pressure and catecholamine responses in men (Frankenhaeuser et al., 1978, 1980; Matthews and Stoney, 1988; Lepore et al., 1993; Becker et al., 1996; Steptoe et al., 1996; Traustadóttir et al., 2003; Matthews et al., 2001), while heart rate responses are more pronounced in

women (Matthews and Stoney, 1988; Tersman et al., 1991; Heponiemi et al., 2004; Kudielka et al., 2004a). The data from these studies also suggest that the age and hormonal status of the women have marked effects on autonomic responses.

Some studies suggest that there are sex differences which are dependent on the nature of the stressor used. For example, a study of 17-23-year-old subjects including 26 women in random menstrual phase and 24 men showed that men exhibit a higher salivary cortisol response to achievement-oriented challenges such as mathematics and verbal tasks while women respond more intensely to social rejection (Stroud et al., 2002). Although such a difference would have considerable methodological implications, it has not been replicated in a corresponding setting and importantly the TSST elicits consistent HPAA and autonomic nervous system responses in both sexes.

#### 3.1. Infancy and childhood

Despite the considerable literature about cortisol reactivity during infancy, few studies have reported any sex differences. Davis and Emory (1995) have studied the response of infants to the Brazelton developmental assessment before 3 days of age and shown clearly higher salivary cortisol response in male and marginally higher heart rate response in female infants. A series of studies have measured behavioural response and salivary cortisol after routine inoculation at 2-6 months of age. These authors conclude that their data indicate comparable results in both sexes but do not characterise these in detail (Ramsay and Lewis, 1994). A study of 23 male and 32 female infants and toddlers sampled throughout a day at day-care and home showed no other difference than a higher value in girls at afternoon (Watanura et al., 2003). Although the finding of no sex difference is supported by studies using non-stimulated salivary cortisol concentrations (Kiess et al., 1995) or a maximal stimulation of the adrenal cortex by 250 µg ACTH<sub>1-24</sub> (Lashansky et al., 1991), the possible effects of the peculiar sex steroid milieu of early infancy, with a transient high testosterone peak in male infants, clearly merits further study.

Neither is there any conclusive evidence on sex differences in stress responsiveness during childhood, despite the potential of life-long effects of HPAA activation by social challenges during this period (Gunnar and Donzella, 2002). Data on 16 boys and 15 girls aged 9-15 years showed similar salivary cortisol responses to TSST modified for

**Table 1** Studies describing sex differences in physiological response to acute psychosocial stress in adults.

Reference	Age	Males + females	Cycle days	Design/aim	Stressor	Effects on stress responsiveness								
						HPAA			Autonomic nervous system					
						Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure	Epinephrine	Norepinephrine	Other	
Kirschbaum et al. (1999)	18-32 years	20 + 61	4-7	20 men, 19 follicular women	TSST	Men vs. follicular phase women	M	→	M					
			21-25	21 luteal women		Men vs. luteal phase women	→	→	M					
			RND	21 women with oral contraceptives (monophasic)		Men versus women with OC	M	→	M					
Kudielka et al. (2004b)	9-15 years	16 + 15		Reanalysis of previous studies	TSST	9-15 years	→							
	19-32 years	20 + 21	21-25			19-32 years	→	→	M				CBG: →	
	60-76 years	15 + 15	PM			60-76 years	M	F	→				CBG: F	
Kudielka et al. (2004a)	9-15 years	28 <sup>a</sup>		Reanalysis of previous studies	TSST	9-15 years				F			Children and elderly adults: females show slower recovery	
	19-32 years	34 <sup>a</sup>	21-25			19-32 years				F				
	60-76 years	26 <sup>a</sup>	PM			60-76 years				→				
Kudielka et al. (1998)	59-81 years	39 + 36	PM	DHEA 50 mg/ placebo for 2 weeks	TSST		M	M	M	→	→	→		
Wolf et al. (2001)	Uni students	14 + 8	21-25	Effects of stress-induced cortisol on memory	TSST		→						Cortisol response inversely correlated with declarative memory but only in males	
Kirschbaum et al. (1992)	19-33 years	65 + 70	RND	Comparison of TSST with anticipation, CRH test and ergometry	TSST		M						CRH test and ergometry produced similar cortisol response in both sexes	
		9 + 9			TSST anticipation only		M							

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**Table 1** (continued)

Reference	Age	Males + females	Cycle days	Design/aim	Stressor	Effects on stress responsiveness									
						HPAA			Autonomic nervous system						
						Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure	Epinephrine	Norepinephrine	Other		
Rohleder et al. (2001)	Mean 25 y	18 + 27	22-27	Main focus effects of TSST on immune parameters	TSST	→									Sex differences in LPS-stimulated and glucocorticoid-inhibited cytokine production
Kirschbaum et al. (1996b)	Students	5 + 8	NR	Effect of cortisol on memory	TSST	M									Cortisol response inversely correlated with declarative memory
Kirschbaum et al. (1995)	19-29 years	32 + 34	RND	No support/support by stranger/support by partner; 25 women in follicular, 11 in luteal phase	TSST	M									Support by partner attenuated response in men but increased it in women
Earle et al. (1999)	Uni students	28 + 32	NR	Math task, half of the subjects harassed during the task	Math only	→			→	→					
					M + harassment	M			→	→					
Larson et al. (2001)	18-59 years	19 + 37	RND	One woman postmenopausal; blood sampling too early to observe rise in cortisol	Speech	→			→	→					NKCA, IFN $\gamma$ , IL-10 all →
Nicolson et al. (1997)	40-59 years	6 + 10	PM	Comparison of three age groups	Speech	M									
	60-69 years	10 + 10				→									
	≥ 70 years	10 + 10				→									
Lepore et al. (1993)	College students	43 + 47	NR	Alone/with supportive or non-supportive confederate	Speech					M					Presence of a non-supportive confederate augments the response in both sexes



Stephoe et al. (1996)	30-40 years	29+30	NR	Effect of age and sex	Visual problem-solving mirror drawing Speech		M		M	M					BP response is correlated with adverse lipid profile in old men
	55-65 years	35+38	PM				M		→	→					
Seeman et al. (1995)	70-79 years	12+14	PM	Sex differences in elderly subjects	Driving simulation			→	→						Women have higher joint increase in ACTH and cortisol
Seeman et al. (2001)	22-36 years	9+17	NR	Sex differences in age-related changes	Stroop memory		M								
	67-88 years	7+7					F								
Owens et al. (1993)	40-55 years	15+34	RND	Comparison between sexes and pre- and post-menopausal women	Mirror-image speech	Men compared with: premenopausal women			→	→	→	→			
						Postmenopausal women		→	→	F	→	→			
Becker et al. (1996)	45-73 years	14+15	NR	Detailed assessment of cardiovascular function by radionuclide ventriculography in healthy subjects	Stroop speech			→	→	M	M	M			LV function → EF →
Matthews and Stoney (1988)	31-62 years	93+125	NR	Sex differences in adults and children	Math mirror drawing hand-grip				F	M					High school children showed similar sex differences
Stoney et al. (1990)	18-29 years	11+19	5-10	Change of lipids and lipoproteins during stress	Math speech				F	M	→	→			LDL cholesterol increase greater in males
Matthews et al. (2001)	24-46 years	31+31	NR	Main focus effects on chronic stress on acute stress responsiveness	Math speech			→	→	M	M	→			Low levels of chronic stress are associated with high SBP and epinephrine responses in men but not in women

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Table 1 (continued)

Reference	Age	Males + females	Cycle days	Design/aim	Stressor	Effects on stress responsiveness								
						HPAA			Autonomic nervous system					
						Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure	Epinephrine	Norepinephrine	Other	
Heponiemi et al. (2004)	22-37 years	35 + 41	NR	Main focus the effect of behavioural activation/inhibition	Math reaction time speech				F					RSA →; PEP →
Tersman et al. (1991)	21-40 years	15 + 15	5-7; 24-26	Each subject assessed twice, females in both menstrual phases	Math <sup>b</sup> cold pressor		M		F	→				Serum aldosterone: luteal phase > follicular phase = men
Traustadóttir et al. (2003)	55-75 years	8 + 7	PM	Sex differences in elderly subjects	Stroop math verbal cold pressor interview		M	→	→	M				
Ward et al. (2004)	26 years	103 + 76	RND incl. OC	Relation between size at birth and stress response	Stroop mirror drawing speech				NR	M				Birth weight inversely correlated with blood pressure and heart rate response in women but not in men
Thorsteinsson et al. (1998)	18-35 years	20 + 20	NR	Main aim to study the effect of social support	Video game with or without video-relayed social support	→			→	M				Support attenuated HR and cortisol responses in both sexes
Frankenhaeuser et al. (1978)	18-19 years	19 + 30	RND	Matriculation exam (essay) and normal school day	Matriculation examination		→ <sup>c</sup>				M <sup>c</sup>	→ <sup>c</sup>		MHPG <sup>c</sup>
Frankenhaeuser et al. (1980)	18-34 years	24 + 24	NR	12 + 12 type A 12 + 12 type B	Choice-reaction at own pace		→ <sup>c</sup>		→		M <sup>c</sup>	→ <sup>c</sup>		
Stroud et al. (2002)	17-23 years	24 + 26	RND	Comparison of achievement-oriented task and social rejection scenario	Math verbal memory social rejection	Achievement (=math + memory)	M							
					Social rejection		F							



Malarkey et al. (1994)	Newlywed	90 + 90	5-9	Marital conflict	Couple attending a problem-solving or conflict task together	M	F	↑	Epinephrine levels associated with hostility more strongly in women
CBG, corticosteroid-binding globulin; EF, ejection fraction; IFN $\gamma$ , interferon gamma; IL-10, interleukin-10; LV, left ventricular; MHPG, 3-methoxy-4-hydroxyphenylethylene, a metabolite of epinephrine and norepinephrine; NKCA, natural killer cell activity; NR, not reported; OC, oral contraceptives; PEP, pre-ejection period, a short PEP being a sign of sympathetic activity; PM, postmenopausal; RND, random; RSA, respiratory sinus arrhythmia, a sign of parasympathetic activity; TSST, Trier Social Stress Test; M, higher in males; F, in females; $\rightarrow$ , no difference.									
a Total number in each age group; number of males and females not reported.									
b Results presented in this table refer to the mathematics test.									
c Urinary cortisol, epinephrine, norepinephrine and MHPG.									

children, levels being comparable to those in adults (Kudielka et al., 2004b). No differences in urinary cortisol, epinephrine or norepinephrine were seen in a group of about 30 3-year-old children during a follow-up day at hospital (Lundberg et al., 1981).

In a study of 103 prepubertal boys and 11 girls, whose fathers were drug addicts, an auditory event-related potential measurement was used as a stressor. Compared with control children, children of drug-dependent fathers showed regardless of sex overall lower salivary cortisol responses, although among these children salivary cortisol levels were higher in girls, both before and after the stressor (Hardie et al., 2002).

As to cardiovascular responses, children in general show lower blood pressure reactivity than adults (Matthews and Stoney, 1988). As to heart rate, there are reports of a higher response in children (Matthews and Stoney, 1988) or no difference (Kudielka et al., 2004a). A higher heart rate response to the TSST in 9-to-15-year-old girls as compared with boys was reported by Kudielka et al. (2004a) in a reanalysis of data from five previous studies. A study of 76 adolescent females and 56 males repeated after an average interval of four years, consisting of an arithmetic task, mirror tracing and isometric exercise, showed that across adolescence males have a larger increase in systolic and diastolic blood pressure (Matthews et al., 1990). Although the pubertal stage of the study subjects was not reported, the result is likely to indicate differences triggered by pubertal development. It is likely that the study of normal and abnormal pubertal development could provide an excellent setting to study the effects of hormonal changes on stress responsiveness; this area has however been greatly neglected.

### 3.2. Menstrual status

Many of the earlier studies using mild to moderate stressors such as a simulated interview reported similar HPA responses to acute stress regardless of the menstrual cycle phase (Abplanalp et al., 1977). However, the use of standardised stress protocols has brought into light considerable variation, generally with enhanced responsiveness in the luteal phase. These studies are summarised in Table 2. In a study of 15 women studied at days 5-7 and 24-26 of their menstrual cycle, the glucocorticoid response to an arithmetic stressor test was increased in the luteal phase as was the cold pressor response (Tersman et al., 1991). Similar findings were observed in a comparison of 21 women in the luteal phase compared with 19 in

**Table 2** Studies on the effect of menstrual status, pregnancy, lactation, menopause, and treatment with sex steroids on HPA and autonomic stress response.

Reference	Subjects	Design	Stressor	Measurements	Effects on stress responsiveness						
					HPAA			Autonomic nervous system		Other	
					Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure		
<b>Menstrual status</b>											
Kirschbaum et al. (1999)	Women 18-32 years ( <i>n</i> =61)	19 follicular women (cycle days 4-7); 21 luteal women (cycle days 21-25)	TSST	Luteal vs. follicular phase	↑	→	→	→			
Abplanalp et al. (1977)	Women 21-38 years ( <i>n</i> =21)	Nine women at cycle days 1-6 compared with 12 women at cycle days 7-21	Interview			→					GH →
Tersman et al. (1991)	Women 21-40 years ( <i>n</i> =15)	Each subject participated during cycle days 5-7 and 24-26	Math cold pressor <sup>a</sup>	Luteal vs. follicular phase		↑		→	→		Serum aldosterone ↑
Sita and Miller (1996)	Women 18-35 years ( <i>n</i> =30)	Each subject participated during cycle days 7-11 and 17-21	Speech shock avoidance cold pressor	Luteal vs. follicular phase				→	→		CO →; PEP →; TPR → <sup>b</sup>
Rohleder et al. (2003)	Women 23 years ( <i>n</i> =25)	11 during cycle days 22-27; 14 using OC	TSST	Luteal phase vs OC users	↑						Glucocorticoid sensitivity of pro-inflammatory cytokine production ↓
<b>Oral contraceptives</b>											
Kirschbaum et al. (1995)	Women 19-29 years ( <i>n</i> =34)	12 follicular women; 11 luteal women; nine women with oral contraceptives (any regimen); (cycle days not reported)	TSST	OC use vs. non-use	→						Study designed to assess the effect of social support, not OC

Kirschbaum et al. (1999)	Women 18-32 years (n=61)	19 follicular women (cycle days 4-7); 21 luteal women (cycle days 21-25); 21 women with oral contraceptives (monophasic)	TSST	OC vs. luteal phase	↓	→	→	→			
				OC vs. follicular phase	→	→	→	→			
				OC vs. luteal phase	↓						
Rohleder et al. (2003)	Women 23 years	21 luteal women (cycle days 22-27); 14 women with oral contraceptives								Glucocorticoid sensitivity of pro-inflammatory cytokine production ↑	
Ward et al. (2004)	Women 26 years (n=76)	37 women in random menstrual phase; 39 women with oral contraceptives	Stroop mirror drawing speech	OC vs. no OC					→		
Matthews and Rodin (1992)	Pregnant and non-pregnant women (n=55)	21 women tested before pregnancy and during II trimester; 34 non-pregnant women as controls tested twice	Math mirror image Iso-metric handgrip					→	↓		
DiPietro et al. (2003)	Pregnant women and their fetuses (n=137)	Test performed at 24 and 36 weeks	Stroop	36 vs. 24 weeks					Mat ↓	Greater increase in fetal HRV and decrease in motor activity; the latter greater in male fetuses	
Heinrichs et al. (2001)	Lactating women 6-11 weeks post-partum (n=42)	<b>Lactation</b> Lactating women, either breastfeeding or holding the infant for 15 min	TSST	Breastfeeding vs. holding the infant	↓	↓	→		→	→	Oxytocin → vasopressin → prolactin ↑ <sup>c</sup>

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**Table 2** (continued)

Reference	Subjects	Design	Stressor	Measurements	Effects on stress responsiveness							
					HPAA			Autonomic nervous system		Other		
					Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure		Epinephrine	Norepinephrine
Altemus et al. (2001)	Lactating women 6-24 weeks postpartum and controls ( <i>n</i> =51)	24 lactating; 13 postpartum non-lactating; 14 healthy control	TSST	Lactating vs. postpartum non-lactating		→	→	→	→		Postpartum non-lactating have higher systolic blood pressure and lower RSA throughout the test	
				Lactating vs. controls		→	→	→	→			
Owens et al. (1993)	Pre- and postmenopausal women 40-55 years ( <i>n</i> =34)	<b>Menopause</b> Comparison between sexes and post- and pre-menopausal (random menstrual phase) women	Mirror-image speech	Postmenopausal vs. premenopausal				→	↑	→	→	
Seeman et al. (2001)	Young women 22-36 years ( <i>n</i> =17); elderly women 67-88 years ( <i>n</i> =7)	Comparison of sexes and age; menstrual phase not reported	Memory stroop	Postmenopausal vs. premenopausal	↑							
Stephoe et al. (1996)	Premenopausal women 30-40 years ( <i>n</i> =30); postmenopausal women 55-65 years ( <i>n</i> =38)	Effect of age and sex	Visual problem-solving; mirror drawing speech	Postmenopausal vs. premenopausal	→			↓	↑			
Lindheim et al. (1992)	Premenopausal women 23-41 years ( <i>n</i> =13); postmenopausal women 47-71 years ( <i>n</i> =36)	Comparison of pre- (cycle days 4-9) and postmenopausal women	Math stroop speech cold pressor	Postmenopausal vs. premenopausal	↓	→		↑	→	→		
Traustadóttir et al. (2005)	Premenopausal women 19-36 years ( <i>n</i> =9); postmenopausal women 59-81 years ( <i>n</i> =13)	Comparison of unfit premenopausal (cycle days 3-7) and unfit postmenopausal women	Stroop math verbal cold pressor interview	Postmenopausal vs. premenopausal		↑	→	↓	↑			The study also included 11 postmenopausal fit women whose results were not compared with premenopausal

Kudielka et al. (1999)	Premenopausal women 20-31 years (n=15); postmenopausal women 60-79 years (n=28)	Comparison of pre- (early follicular) and postmenopausal women and the effects of 2 weeks estradiol or placebo patch in postmenopausal women	TSST	Postmenopausal vs. premenopausal	→	→	→	→	→	→	
Kudielka et al. (2004b)	Young women 19-32 years (n=21); elderly women 60-76 years (n=15)	Reanalysis of previous studies; premenopausal women during cycle days 21-25	TSST	Postmenopausal vs. premenopausal		↑	→				
Kudielka et al. (2004a)	Young women 19-32 years (n=approximately 20); elderly women 60-76 years (n=approximately 15)	Reanalysis of previous studies; premenopausal women during cycle days 21-25	TSST	Postmenopausal vs. premenopausal				↓			
Komesaroff et al. (1999)	Perimenopausal women, mean 48 y (n=12)	<b>Estrogen</b> 8 weeks estradiol or placebo, stress before and after the period	Math distractive noise	Estradiol vs. placebo		↓	↓	↓	↓	↓	↓ total NE spillover
Lindheim et al. (1992)	Premenopausal women 23-41 years (n=13); postmenopausal women 47-71 years (n=36)	Comparison of pre- (cycle days 4-9) and postmenopausal women and the effects of 6 week estradiol or placebo	Math stroop speech cold pressor	Estradiol vs. placebo		↓	↓		↓	↓	
				Postmenopausal compared with premenopausal		↓	→		↑	→	→

(continued on next page)

**Table 2** (continued)

Reference	Subjects	Design	Stressor	Measurements	Effects on stress responsiveness							
					HPAA			Autonomic nervous system				
					Salivary cortisol	Plasma cortisol	ACTH	Heart rate	Blood pressure	Epinephrine	Norepinephrine	Other
Kudielka et al. (1999)	Premenopausal women 20-31 years ( $n=15$ ); postmenopausal women 60-79 years ( $n=28$ )	Comparison of pre- (early follicular) and postmenopausal women and the effects of 2 weeks estradiol or placebo patch in postmenopausal women	TSST	Estradiol vs. placebo	→	→	→	→	→	→		
				Postmenopausal compared with premenopausal	→	→	→	→	→	→		
Kirschbaum et al. (1996a)	Men, mean 24 years ( $n=32$ )	Estradiol patch 100 µg/d or placebo for 24 or 48 h	TSST	Estradiol vs. placebo	↑		↑	→			↑	
Del Rio et al. (1994)	Male medical students ( $n=21$ )	Estradiol patch 100 µg/d a day before or placebo, cross-over	Math	Estradiol vs. placebo				↓	↓	↓	↓	FFA, acetoacetate and 3-OH-butyrate resp. ↓; Insulin and glucose → Total NE spillover →
Komesaroff et al., 2002	Men hypogonadal due to treatment of prostate cancer ( $n=12$ )	8 weeks of estradiol supplementation (1 mg) ( $n=7$ ) or placebo ( $n=5$ ) Estrogen + progestogen	Math distractive noise			↓	↓	→	↓	↓	→	
Burleson et al. (1998)	Women 50-80 years ( $n=55$ )	Women receiving estrogen ( $n=16$ ); estrogen + progestogen ( $n=14$ ); or 25 no HRT for > 2 years	Speech math	HRT vs. no HRT		↑	→	↑		→	→	RSA <sup>d</sup> ↑
				Estrogen + progestogen vs. estrogen only		→	→	→		↑	→	RSA <sup>d</sup> ↓

Rohleder et al. (2002)	Young men, mean 25 years ( $n=14$ ); elderly men, mean 68 years ( $n=26$ )	<b>Testosterone</b> 14 young 12 elderly with testo (enanthate 150 mg) 5 days before 14 elderly with placebo DHEA	TSST	Testosterone vs. placebo	→					Glucocorticoid sensitivity of pro-inflammatory cytokine production ↑
Kudielka et al. (1998)	Men ( $n=39$ ) and women ( $n=36$ ); 59-81 years	DHEA 50 mg/ placebo for 2 weeks	TSST	Men	→	→	→		→	
Modell et al. (1990)	Women 22-30 years; hyperandrogenic ( $n=5$ ) and control ( $n=5$ )		Math	Women Hyperandrogenic vs. control	↑	→	→ <sup>e</sup>		→	GH ↓

BP, blood pressure; CO, cardiac output; FFA, free fatty acids; GH, growth hormone; HRT, hormone replacement therapy; NE, norepinephrine; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; TPR, total peripheral resistance; TSST, Trier Social Stress Test.

<sup>a</sup> Results presented in this table refer to the mathematics test.

<sup>b</sup> Estradiol concentrations in luteal phase were correlated with cardiac output responsiveness to speech/video game. Correlations between estradiol/progesterone concentrations and responses to cold pressor test also reported in the paper.

<sup>c</sup> Increase in prolactin response means larger stress-induced reduction in serum prolactin (after a higher baseline value).

<sup>d</sup> Increase in RSA response means larger stress-induced reduction in RSA; decrease means smaller reduction.

<sup>e</sup> Higher plasma cortisol at anticipation and after recovery, no difference immediately after stress.



he follicular phase subjected to the TSST. The salivary cortisol response was clearly enhanced in the luteal phase, with levels comparable to those of men, although ACTH concentrations similar to follicular-phase women suggested that women in the luteal phase may have enhanced adrenal sensitivity (Kirschbaum et al., 1999). The finding of similar salivary cortisol responses to the TSST in men and luteal-phase women has been confirmed in two subsequent studies (Rohleder et al., 2001; Wolf et al., 2001). A study with most women in the follicular phase of their cycle showed lower salivary cortisol responses to a TSST compared with men (Kirschbaum et al., 1995).

Regarding the autonomic nervous system, a carefully conducted study of 15 women each studied in the menstrual, follicular and luteal phases, with speech, arithmetic and isometric exercise tasks as stressors, failed to show any relationship between menstrual phase and cardiovascular response or urinary or plasma catecholamines (Stoney et al., 1990). Also no difference in the response of various cardiovascular parameters to speech, shock avoidance and cold pressor was found in 30 women studied in the follicular and luteal phases (Sita and Miller, 1996).

From a methodological point of view, it is important to take the menstrual phase of subjects into account in study design. The failure to do this may explain why some studies show no difference in stress responsiveness according to sex (for example, Frankenhaeuser et al., 1978, 1980; Owens et al., 1993; Thorsteinsson et al., 1998; Matthews et al., 2001; Larson et al., 2001).

### 3.3. Oral contraceptive use

The use of oral contraceptives has clear effects on the physiological response to psychosocial stress (Table 2). Kirschbaum and co-workers have compared reactions to the TSST in women using a monophasic regimen containing less than 50 µg ethinylestradiol (Kirschbaum et al., 1999) with a comparison group of similarly-aged men and women in different menstrual phases. While oral contraceptive users had ACTH and total plasma cortisol response comparable to that of non-users regardless of menstrual phase, their salivary cortisol values, reflecting free circulating cortisol, were lower and comparable with women in the follicular phase. Lower salivary cortisol as compared with the luteal phase was subsequently observed in a similar setting (Rohleder et al., 2003), although this finding was not seen in a previous study which however was designed to assess the effect of social support, not

oral contraceptive use (Kirschbaum et al., 1995). A key mechanism is likely to be the estrogen-induced increase in corticosteroid-binding globulin (CBG) (Moore et al., 1978). However, the picture is complicated by the evidence that the reduced free cortisol concentrations may be accompanied by increased glucocorticoid sensitivity, at least as assessed by pro-inflammatory cytokine production (Rohleder et al., 2003).

Not many studies have assessed the effect of oral contraceptives on autonomic nervous system response to psychosocial stress. In 26-year-old women, mean blood pressure response to a stressor consisting of Stroop, mirror drawing and speech tasks was similar in 39 oral contraceptive users as compared with 37 non-users in random menstrual phase (Ward et al., 2004). However, sympathetic and cardiovagal baroreflex sensitivity, as assessed by relating muscle sympathetic nerve activity and heart rate to blood pressure after sodium nitropruside and phenylephrine injections, have been found to be higher during the 7-day placebo phase than the 21-day ethinyl estradiol phase of the cycle (Minson et al., 2000).

### 3.4. Pregnancy and lactation

During pregnancy, there are major changes in the physiology of the HPA (Mastorakos and Ilias, 2003; Lindsay and Nieman, 2005; de Weerth and Buitelaar, 2005). Abundant production of CRH by intrauterine tissues leads to exponential increase in the plasma levels of CRH (McLean et al., 1995; Challis et al., 2000). Maternal pituitary ACTH secretion and plasma ACTH levels rise and are paralleled by adrenal hypertrophy and a rise in plasma total cortisol levels. Although there is a marked rise in the circulating concentrations of CBG, free (unbound) cortisol concentrations are somewhat elevated. Correspondingly, the autonomic nervous system undergoes significant alterations during pregnancy. These are characterised by increased sympathetic activity and decreased high-frequency heart rate variability, probably indicating reduced parasympathetic function (Ekholm and Erkkola, 1996).

The reactivity of both the HPA and sympathoadrenal components of the stress response are dampened during pregnancy (de Weerth and Buitelaar, 2005). Women exposed to both psychological (mental arithmetic and mirror tracing) and physical (isometric handgrip) stressors had lower blood pressure responses during the second trimester of pregnancy compared with their pre-pregnancy responses (Matthews and Rodin, 1992).

During the third trimester of pregnancy, epinephrine and vasoconstrictor responses to the cold pressor test are reduced as compared to after delivery (Nisell et al., 1985), as are heart rate and norepinephrine responses to standing and isometric handgrip (Barron et al., 1986). Although we are unaware of any published data on HPA responses to psychological stressors, the response to pharmacological stimulants is reduced. For example studies using a standard CRH test during the third trimester of pregnancy showed an absence of ACTH responses which were shown to recover postpartum (Schulte et al., 1990). Intriguing data based on the follow-up of women who were exposed to an earthquake during pregnancy suggest that the psychological and physiological consequences of severe stress are different according to the stage of pregnancy. This study showed that not only was the effect of the earthquake perceived to be more stressful when it occurred during the first trimester of pregnancy, but that the effect on the offspring (measured by the reduction in gestational length) was progressively diminished in the later trimesters of pregnancy (Glynn et al., 2001).

Data on the effects of lactation on physiological response to psychosocial stress are limited to two studies. The acute effects of lactation were studied in 42 women who were randomised to groups either breast-feeding or holding their infants for 30 min before the TSST (resulting in higher prolactin levels at the onset of the test). After lactation, salivary and plasma total cortisol responses were reduced, whereas ACTH, vasopressin, epinephrine, norepinephrine and oxytocin responses were similar (Heinrichs et al., 2001). Another study compared postpartum lactating women, studied 1 h after breast feeding, with non-lactating postpartum women and non-postpartum controls. There were no differences in plasma ACTH and total cortisol concentrations as well as heart rate and blood pressure responses to the TSST. However, non-lactating postpartum women had overall higher systolic blood pressure and lower respiratory sinus arrhythmia, indicating lower parasympathetic tone (Altemus et al., 2001).

### 3.5. Menopause and treatment with sex steroids

In addition to menstrual cycle, menopause and postmenopausal hormone replacement therapy provide obvious natural experiments to study the effects of the hormonal environment on stress responsiveness. In general, postmenopausal women tend to show enhanced cardiovascular, in

particular blood pressure responses, while the findings regarding the HPA are somewhat inconsistent (Table 2). Moreover, it is of note that in many cases a similar age-related increase in stress responsiveness is seen in men in whom the decline in sex steroid concentrations is much more gradual.

A study comparing 36 postmenopausal women with 13 premenopausal women in their early follicular phase found increased systolic blood pressure responsiveness during an arithmetic and speech tasks in the postmenopausal women. This response was attenuated after 6 weeks of transdermal estradiol treatment. The plasma total cortisol response, however, was lower in postmenopausal women, and it was further attenuated after estradiol but not after placebo treatment (Lindheim et al., 1992). This finding may however be partly due to the fact that the test, although placebo-controlled, was repeated in the same subjects introducing the possible effect of habituation. The finding is in contrast with observations demonstrating that, in comparison to premenopausal women, elderly women show elevated salivary cortisol after Stroop and memory challenges (Seeman et al., 2001) and elevated plasma total cortisol after the TSST (Kudielka et al., 2004b) or the Matt Stress Reactivity Protocol consisting of Stroop, arithmetics and verbal tasks followed by cold pressor challenge and interview (Traustadóttir et al., 2005). Likewise, no gender difference in salivary cortisol responses to a speech task was observed in groups of 60 to 69 or 70-year-old and over subjects, whereas in 40-59-year-olds men had a higher response (Nicolson et al., 1997). Men and women aged 70-79 had similar plasma ACTH and total cortisol responses to a driving simulation, although a combined increase in the concentrations of both was more frequent in women (Seeman et al., 1995). In an informative study of Owens et al. (1993) a group of 16 postmenopausal women showed increased blood pressure responses to mirror tracing and speech tasks in comparison with equal-sized groups of men and premenopausal women of mixed menstrual phase. Postmenopausal women, furthermore, had higher ambulatory blood pressure during a working-day, levels being similar to those in men. The magnitude of blood pressure rise was as well correlated with serum total cholesterol levels. Results are consistent with a study of 38 postmenopausal women who, compared with 30 premenopausal women, showed increased blood pressure responses to a similar set of stressors (Steptoe et al., 1996). Heart rate response, by contrast, is usually lower in postmenopausal women (Steptoe et al., 1996; Kudielka et al., 2004a;

Traustadóttir et al., 2005), or no difference is observed (Owens et al., 1993).

Kudielka et al. (2004b) reanalysed data from previous studies (Buske-Kirschbaum et al., 1997, 2003; Kudielka et al., 1999, 2000; Kirschbaum et al., 1999) which had used the TSST as stressor. They concluded that, compared with premenopausal women in their luteal phase, postmenopausal women show a similar rise in ACTH accompanied by a much higher rise in total plasma cortisol. This, however, resulted in a similar rise in salivary cortisol, perhaps in part because of lower CBG concentrations after menopause.

The study of how the response to stress testing changes after the use of hormone replacement therapy offers an opportunity to assess the role of estrogen on stress responsiveness in postmenopausal women. However, the acute effects of administered estrogen on the stress responsiveness appear to be complex. The outcome appears to depend on baseline hormonal levels, the nature of the stressor, and possibly the life-long effects of intrauterine exposure to sex steroids. A study of 12 perimenopausal women randomised to receive a 8-week course of oral estradiol or placebo showed that estrogen administration led to reduced blood pressure, ACTH, cortisol and catecholamine responses to an arithmetic test (Komesaroff et al., 1999). A study comparing 50-80-year-old subjects with or without oral hormone replacement therapy over a 2-year period showed that both estrogen or estrogen-progestin combination therapy were associated with an increase in vagal withdrawal, as assessed by respiratory sinus arrhythmia, and increased plasma total cortisol response to arithmetic and speech challenges (Burlison et al., 1998).

## 4. Possible mechanisms

### 4.1. HPAA

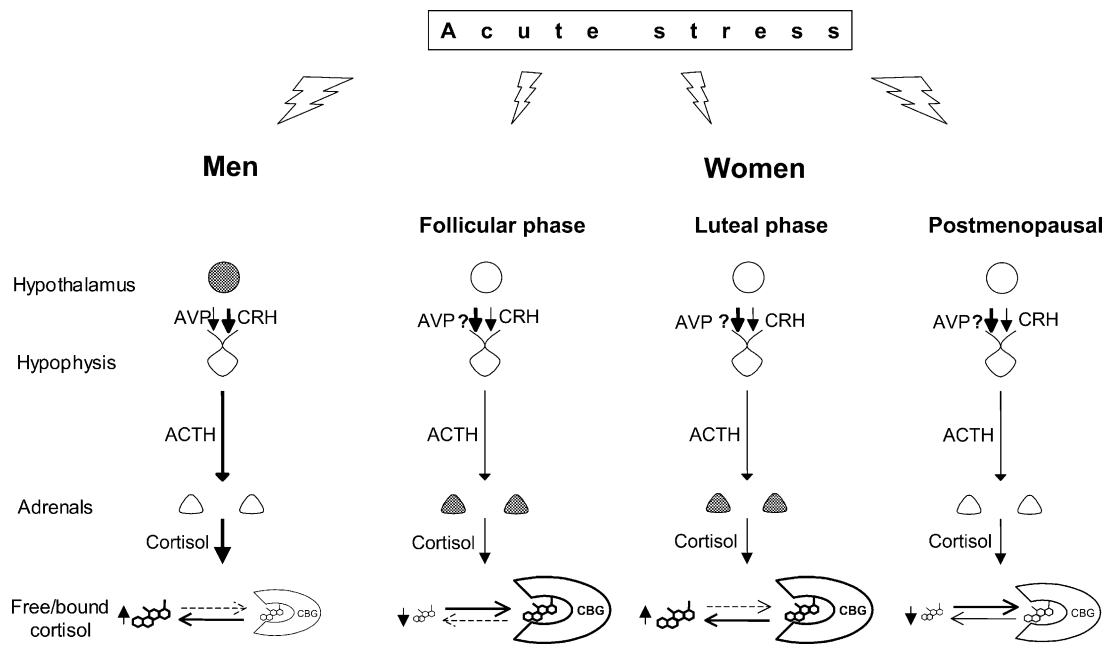
The use of psychological stress stimuli such as public speaking tasks are probably the best approximations to real-life stressors. Studies using these methods have consistently shown pronounced sex differences in the physiological stress response. However, it is of note that these stressors stimulate the HPAA at the central level and do not necessarily distinguish between different levels of the axis. Such data are however obtainable from studies using specific biochemical tests of the HPAA.

#### 4.1.1. Level of HPAA

Fig. 1 summarises the current understanding on sex differences in the function of the HPAA during the stress response. Studies estimating the secretory rate of ACTH and cortisol in normal conditions obtained by frequent blood sampling present convincing evidence on sex differences. Small studies have found increased 24-h ACTH secretion in men, compared with women in the early follicular phase, which was attributable to an increase in pulse amplitude (Horrocks et al., 1990; Roelfsema et al., 1993) and possibly frequency (Horrocks et al., 1990). Yet, these studies showed no sex difference in cortisol secretion, suggesting that the female adrenal cortex is more responsive to physiological concentrations of ACTH than its male counterpart. However, maximal adrenal cortex stimulation by 250 µg ACTH<sub>1-24</sub> produces similar plasma total cortisol response in both sexes, in females regardless of menstrual phase (Kirschbaum et al., 1999), suggesting a similar maximum capacity of the adrenal cortex. Studies using a hCRH test show in general no sex differences at the pituitary level at least before menopause (Kirschbaum et al., 1992; Born et al., 1995). These observations suggest that sex differences in HPAA responsiveness can be attributed to central differences as well as differences in the adrenal responsiveness to ACTH.

#### 4.1.2. AVP

Differences in arginine vasopressin (AVP) secretion may also explain sex differences in HPAA function. AVP is a nonapeptide produced by magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus with both peripheral, vasoconstrictor and antidiuretic, and neuroendocrine actions, including potentiation of CRH-evoked ACTH-release in the pituitary (Gillies et al., 1982). AVP production and responsiveness is known to exhibit sex differences at several levels of the HPAA. In a CRH stimulation test combined with AVP administration, young women show greater plasma ACTH and total cortisol responses compared with men (Born et al., 1995), indicating an increased sensitivity of the female pituitary to AVP. Interestingly, despite dexamethasone suppression, strenuous physical exercise results in higher plasma AVP and total cortisol (but not ACTH) responses in women (Deuster et al., 1998). As AVP has been shown to directly stimulate cortisol secretion in the adrenal cortex (Perraudin et al., 1993), this finding may reflect not only an increase in AVP responsiveness to exercise but also an increased cortisol response to AVP.



**Figure 1** HPA stress responsiveness in adulthood according to sex, menstrual and menopausal status. Bolded arrows and larger cortisol molecules indicate increased concentrations. Increased sensitivity of the CRH production of the male hypothalamus to stress, indicated by shading, leads to increased ACTH synthesis. The premenopausal female adrenal cortex is however more sensitive to ACTH (as indicated by shading) counterbalancing the lower ACTH concentrations and reducing the sex difference in cortisol synthesis. Cortisol bioavailability is further affected by corticosteroid binding globulin (CBG) the synthesis of which is stimulated by estrogen. In addition to the changes shown here, other important determinants of HPA activity include age in both men and women as well as the use of oral contraceptives in women.

#### 4.1.3. CBG

A major part of circulating cortisol is bound to plasma proteins, mostly corticosteroid-binding globulin (CBG). According to the free hormone hypothesis, only the unbound fraction (in typical circumstances about 10% of total cortisol) is metabolically active. CBG synthesis is stimulated by estrogens (Moore et al., 1978) and, consequently, is higher in premenopausal women than men of a similar age (Fernandez-Real et al., 2002) and increases in particular during the use of oral contraceptives (Fujimoto et al., 1986; Wiegratz et al., 2003). This may be one explanation for the higher bioavailability of circulating cortisol suggested by a study in 767 middle-aged men and women showing higher salivary cortisol at 08:00 and 16:00 h in men (Brandtstädter et al., 1991). CBG concentrations may be particularly important during the poststress increase in cortisol when CBG binding sites may become saturated.

#### 4.1.4. Regulation by sex steroids

Physiological differences in estrogen levels are likely to explain many of the pronounced differences in stress responsiveness associated with sex, age and menstrual status. Estrogen concentrations are high in women during the luteal phase, and in

men many of the actions of testosterone in the brain and pituitary are mediated through the estrogen receptor, after conversion of testosterone to estrogen by intracellular aromatase (de Ronde et al., 2003). The results of experimental studies have, however, been conflicting. Young men indeed show a clearly increased plasma ACTH and salivary cortisol response to TSST after a 1- or 2-day treatment with estradiol (Kirschbaum et al., 1996a), and postmenopausal women using oral hormone replacement therapy (either estrogen or estrogen plus a progestogen) have a higher plasma total cortisol response after a public speaking test (Burlinson et al., 1998). However, other studies have shown a decrease in plasma ACTH and total cortisol response. This has been shown after maths task accompanied by distractive noise in hypogonadal elderly men (Komesaroff et al., 2002) and postmenopausal women (Komesaroff et al., 1999), and after a stressor consisting of a mathematical task, a Stroop test, public speaking and cold pressor stimulation in postmenopausal women (Lindheim et al., 1992), all after 6-8 weeks' treatment with estrogen as compared with placebo. In addition, Kudielka et al. (1999) did not observe any difference in plasma ACTH or cortisol or salivary cortisol response to TSST in postmenopausal women after a



two-week transdermal estradiol treatment, as compared with placebo. Neither did a dose of testosterone enanthate 5 days before the TSST have any effect on salivary cortisol response in elderly men (Rohleder et al., 2002). The reasons for these discrepancies remain unclear. Possibilities include differences in the nature of the stressor, in hormone levels before or during treatment, or in the duration of the treatment. Moreover, Komesaroff et al. (1999, 2002) and Lindheim et al. (1992) performed the testing twice and thus actually compared the effect of habituation between estrogen and placebo-treated individuals.

Some insight to this complexity is provided by the extremely multifaceted actions of estrogen in the brain. In rats, estrogen, as well as progesterone, exert complicated regulatory effects on brain glucocorticoid and mineralocorticoid receptors, resulting in both down- and up-regulation of stress responsiveness depending on menstrual phase and the region of brain in question (Peiffer et al., 1991; Burgess and Handa, 1992; Patchev et al., 1995). Estrogen actions are mediated by an array of receptors comprising nuclear receptors estrogen receptor (ER)- $\alpha$  and - $\beta$ , the latter in many cases inhibiting gene transcription mediated by estrogen responsive elements, plus a number of nuclear and membrane-bound estrogen-binding receptors the role of which in explaining these sex differences remains poorly elucidated (Toran-Allerand, 2004). There are pronounced differences in the distribution of ER- $\alpha$  and ER- $\beta$  in some hypothalamic regions, in particular the AVP-expressing cells of the paraventricular nucleus (PVN) where, at least in rodents, ER- $\beta$  is abundantly present while ER- $\alpha$  is barely if at all expressed (Alves et al., 1998; Laflamme et al., 1998). Estrogen reduces AVP expression (Shapiro et al., 2000), an effect which is abolished in ER- $\beta$  knockout mice (Nomura et al., 2002). As to CRH expression, there is rather little overlap in the expression of CRH and ER- $\beta$  in the PVN (Alves et al., 1998), and the effects of estrogen on PVN CRH synthesis are similar in ER- $\beta$ -knockout as in wild type mice (Nomura et al., 2002). This together with the several estrogen-receptor-inducible elements (Vamvakopoulos and Chrousos, 1993) in the promoter region of the CRH gene argues for a key role of ER $\alpha$  in mediating the effects of estrogen on CRH synthesis in the PVN. Indeed, in female rats (Patchev et al., 1995) and in rhesus monkeys (Roy et al., 1999), estrogen stimulates CRH synthesis in the PVN. This framework offers a possible explanation for the discrepancies in studies on the effects of estrogen on the response to psychosocial stress: an attenuating effect could be explained by an ER- $\beta$ -mediated decrease in AVP and

a stimulating effect by ER- $\alpha$ -mediated increase in CRH. Testing this hypothesis requires further study. In addition to these central effects, the stimulation of CBG synthesis (Moore et al., 1978) by estrogen would be expected to reduce the bioavailability of circulating cortisol.

#### 4.1.5. Intrauterine programming of HPA axis responsiveness

It is well established that many of the sexual dimorphisms in brain structure and function are initiated by early, usually fetal exposures to sex steroids (Rhodes and Rubin, 1999). A set of experiments in rats suggests that early hormonal exposures have a central role to play in explaining sex differences in stress responsiveness. Neonatal estrogenisation of female rats is able to cause persistent and profound alterations in neural circuits controlling the HPA axis: elevated CRH and AVP mRNA concentrations in the PVN and reduced GR mRNA in the hippocampus. In addition, it results in a male-like responsiveness to adult estrogen administration, suggesting a programming effect of both HPA axis function and estrogen sensitivity (Patchev et al., 1995; Rhodes and Rubin, 1999).

## 4.2. Autonomic nervous system

### 4.2.1. Autonomic cardiovascular regulation

A key regulator of cardiovascular reactivity is the balance between sympathetic and parasympathetic tone. This is commonly evaluated on the basis of variance components of heart rate and, occasionally, other hemodynamic variables, derived from spectral analysis of beat-to-beat monitoring. Although the theoretical background is relatively complicated, high (breathing-) frequency variance component powers are considered to arise from parasympathetic activity and lower-frequency components from sympathetic tone.

The existing studies in general have shown that women have greater high-frequency variance components or higher ratio of high to low-frequency components suggesting higher proportion of parasympathetic activity (Liao et al., 1995; Evans et al., 2001). This has further been supported by a comprehensive study (Evans et al., 2001) assessing the effect of beta- and muscarinic blockades on the spectral analysis of different hemodynamic variables in young adult men and follicular-phase women. The authors of this study conclude that there is a predominance of sympathetic vascular regulation in men as compared with a dominant parasympathetic influence on heart rate regulation in women. The ratio of parasympathetic to

sympathetic activity decreases with increasing age in both sexes, more clearly so in women (Liao et al., 1995).

#### 4.2.2. The role of sex steroids

There is considerable evidence from clinical studies suggesting that estrogen is involved in the regulation of autonomic stress responsiveness. In most settings, estrogen has had an attenuating effect on sympathetic activity although there are examples of the opposite as well. Postmenopausal women show a higher increase in blood pressure after a TSST-like test (Owens et al., 1993) or a challenge consisting of maths, Stroop, public speaking and cold pressor (Lindheim et al., 1992). This effect is decreased by estrogen supplementation (Lindheim et al., 1992). Attenuated heart rate, blood pressure and catecholamine response after estrogen has been shown after a 1-day treatment with transdermal estradiol in young males exposed to a mental arithmetics stressor (Del Rio et al., 1994) as well as after a 8-week treatment in postmenopausal women exposed to a mental arithmetics challenge with distractive noise (Komesaroff et al., 1999). During the luteal phase, higher estradiol concentrations are associated with lower cardiac output responses to a speech task and video game and lower heart rate and systolic blood pressure responses to cold pressor stimulation (Sita and Miller, 1996). The administration of a single dose of 17 $\beta$ -estradiol to postmenopausal women results in increased ratio of high to low-frequency heart rate variability components (Kaya et al., 2003). Contrasting findings include an increased norepinephrine response and no change in heart rate response to the TSST in young males after a 24-48 h treatment with transdermal estradiol (Kirschbaum et al., 1996a) and no change in heart rate or catecholamine responses after 2 weeks of transdermal estradiol in postmenopausal women (Kudielka et al., 1999).

These discrepancies may in part be explained by the diverse roles of estrogen in modulating autonomic responsiveness, which has been well studied in experimental conditions (Du et al., 1995; Saleh et al., 2000; Saleh and Connell, 2003). Many of the known mechanisms point to a reduction in sympathetic and an increase in parasympathetic nervous system activity. Systemic estrogen administration inhibits the release of norepinephrine and promotes choline acetyltransferase activity (reviewed by Du et al., 1995). In both male and female rats, direct injection of estrogen into several central autonomic nuclei results in increased parasympathetic and decreased sympathetic tone as measured directly from the vagal

and renal sympathetic nerves (Saleh et al., 2000; Saleh and Connell, 2003). Both the sympathetic and parasympathetic effects are blocked by simultaneous administration of an estrogen antagonist. Interestingly, an NMDA receptor antagonist is able to block the effects of estrogen on parasympathetic tone, while the sympathetic effects can be blocked by administering a GABA<sub>A</sub> receptor antagonist (Saleh and Connell, 2003), suggesting that the effects of estrogen on the autonomic nervous system are mediated at least in part through these neuronal pathways.

Much less is known about the effects of progesterone and testosterone on the autonomic nervous system. Clearly, many of the effects of testosterone are mediated through estrogen receptors after conversion to estradiol by intracellular aromatase (de Ronde et al., 2003), but the regulation of this process and possible actions through androgen receptors remain poorly elucidated.

## 5. Evolutionary benefit—a hypothesis

Despite the recent advances in the understanding of mechanisms behind these profound sex differences, their ultimate cause remains poorly understood. In human biology, explanations for complex phenomena are often provided by teleological considerations—consideration of the evolutionary advantage of developing sex differences in behavioural and metabolic responses during stressful situations. Many such evolutionary pressures, such as those related to mating behaviour, are likely to have been diverse and changing over time in different evolutionary contexts. A universal evolutionary requirement, however, is to promote optimal growth and development of the fetus, including buffering the effects of excess maternal stress and, perhaps, to facilitate optimal transfer of information about the prevailing environmental conditions to allow the fetus to fine-tune its metabolic needs to adapt to these conditions (Kaiser and Sachser, 2005). In this section, we propose that this pressure has had an important role in developing the sex-specific differences in stress responsiveness, and that some of the sex steroid effects in non-pregnant states may be by-products of this process. To argue for this hypothesis, we first discuss how non-optimal HPA and sympathoadrenal activity could be harmful to the developing fetus. Thereafter, we relate these facts to the role of estrogen during the pregnant and non-pregnant states. If true, this hypothesis would have a

fundamental impact on our understanding of the life-long programming of the fetal HPAA, which has been proposed to be a key mediator linking small size at birth with adult cardiovascular disease and other health outcomes (Edwards et al., 1993; Phillips et al., 1998, 2000; Levitt et al., 2000; Kajantie et al., 2002, 2003a). At the current level of knowledge, the hypothesis remains unproven although highly plausible and testable.

There are several ways in which excess maternal stress response could be harmful to the fetus. Glucocorticoids and the HPAA have several crucial effects on the developing fetus. During pregnancy, maternal circulating cortisol concentrations increase as a result of the production of CRH by the placenta and fetal membranes. In contrast to its effects in the hypothalamus, cortisol stimulates placental CRH release. This leads to a positive feedback loop important in regulating the timing of delivery, which can be predicted by maternal CRH concentrations already at 16-20 weeks of gestation (McLean et al., 1995). Increased glucocorticoid exposure in the mother could thus accelerate this feedback loop and perhaps lead to premature delivery. This assumption is indeed supported by the finding of an increased risk of preterm birth in stressful living conditions (Moutquin, 2003) or shorter duration of gestation after an exposure to an earthquake during the first trimester (Glynn et al., 2001). There is ample evidence from animal studies showing that prenatal social stress and maternal HPAA stimulation are associated with behavioural changes in the offspring such as overactivity and impaired negative feedback regulation (Huizink et al., 2004). Many of these effects are sex-specific, typically characterised by the masculinisation of the female and infantilisation of the male behaviour in adulthood (Kaiser and Sachser, 2005). While in many occasions such effects may serve an adaptive purpose improving coping for example in situations of increased crowding (Kaiser and Sachser, 2005), in present-day industrialised human societies these effects could be potentially harmful to an individual. Although direct evidence from human studies remains sparse, poorer neurodevelopmental outcome in infancy has been shown to be predicted by increased amount of self-reported daily hassles during early pregnancy, high levels of pregnancy-specific anxiety in midpregnancy and high morning salivary cortisol in late pregnancy (Huizink et al., 2003).

Despite the high maternal concentrations, cortisol in the fetal circulation is maintained at several-fold lower levels. This is mostly due to the placental enzyme  $11\beta$ -hydroxysteroid dehydrogenase-2, which converts maternal cortisol to inactive

cortisone and thus protects the fetus from excess glucocorticoid exposure. Its activity and expression is highly variable between individuals (Stewart et al., 1995; Kajantie et al., 2003b). Importantly, the activity and expression are clearly reduced in conditions such as intrauterine growth restriction (Shams et al., 1998; McTernan et al., 2001; Kajantie et al., 2003b) and pre-eclampsia (McCalla et al., 1998), a disorder which affects 3-5% of pregnancies and is characterised by maternal hypertension, proteinuria and frequently placental dysfunction and fetal growth retardation. In animal experiments,  $11\beta$ -HSD2 activity can be inhibited by protein malnutrition (Bertram et al., 2001). All these conditions are thus likely to make the fetus more sensitive to increased maternal HPAA activation. Moreover, maternal depression is associated with increased plasma total cortisol and norepinephrine levels which in turn predict increased levels of these hormones in the newborn as well as poorer neuromotor performance as assessed by the Brazelton scale (Lundy et al., 1999). The adverse effects of excess fetal glucocorticoid exposure are illustrated by animal experiments exposing pregnant animals to exogenous synthetic glucocorticoids. This resulted in the birth of smaller offspring with altered HPAA activity and elevated blood pressure in adulthood (Benediktsson et al., 1993; Lindsay et al., 1996). Although less is known in humans, babies born small have alterations in HPAA activity in adulthood (Phillips et al., 1998, 2000; Levitt et al., 2000; Reynolds et al., 2001; Kajantie et al., 2002, 2003a; Wüst et al., 2005).

It must be emphasised that glucocorticoids are essential for fetal maturation. Even brief glucocorticoid excess can have profound consequences, as demonstrated by the remarkable efficacy of a standard two-dose maternal treatment with betamethasone in reducing the morbidity and mortality associated with premature birth (Crowley, 2003). Moreover, if premature HPAA activity is related to prematurity, HPAA hypoactivity could be expected to increase the risk of postmaturity, which is associated with increased perinatal mortality (Hollis, 2002). The optimal glucocorticoid exposure is thus likely to be a result of a delicate balance, susceptible to disruption by small alterations in its regulators.

The effects of the maternal autonomic nervous system are likely to be significant for fetal development as well. It is well known that pre-eclampsia is associated with increased sympathetic and decreased parasympathetic activity (Schobel et al., 1996; Yang et al., 2000). That variation in maternal autonomic activity may have a significant



impact on the fetus in normal pregnancies is suggested by the finding that a Stroop colour-word-conflict test at 24th and 36th gestational weeks is associated with decreased motor activity and increased heart rate variability in the fetus (DiPietro et al., 2003). The significance of this observation is further underlined by findings that heart rate variability is higher in male fetuses (Pressman et al., 1998) and that an individual's heart rate and its variability during the fetal period is sustained until at least 1 year after birth (DiPietro et al., 2000). Recently, it was shown that low birth weight is associated with increased blood pressure response to psychosocial stress in young adult females but not in males (Ward et al., 2004).

With this background, it seems probable that there is a strong evolutionary pressure to develop mechanisms to attenuate stress responsiveness during pregnancy. The ability of estrogen to reduce the stress response in many contexts make it the most likely candidate for such a mechanism. Estrogen levels rise throughout pregnancy, at term reaching levels 100-fold higher than the highest concentrations reached during the menstrual cycle (Smith, 1996). With regard to autonomic nervous system activity, the evidence is strong. HPAA activity is more complex as estrogen may increase or reduce HPAA responsiveness, as discussed above. Published data on the HPAA response to stress during pregnancy are sparse, and studies in non-pregnant adults have reported either decreased (Lindheim et al., 1992; Komesaroff et al., 1999, 2002), increased (Kirschbaum et al., 1996a; Burleson et al., 1998), or no change in (Kudielka et al., 1999) HPAA response during estrogen treatment. The differences in human studies may however in part be explained by methodological factors (Kudielka and Kirschbaum, 2005). However, it is important to consider the observations suggesting that during pregnancy maternal cortisol secretion is regulated specifically by AVP rather than CRH (Schulte et al., 1990; Magiakou et al., 1996), and that AVP concentrations are relatively low during pregnancy (van der Post et al., 1997). Animal studies suggest that the attenuating effects of estrogen on HPAA responsiveness are mediated through the ER- $\beta$ -silencing of the AVP gene transcription (Alves et al., 1998; Laflamme et al., 1998; Shapiro et al., 2000; Nomura et al., 2002). Inhibition of AVP synthesis thus offers a plausible mechanism for estrogen to attenuate HPAA function during pregnancy.

The significant effects of the fetal environment on health throughout the life course are increasingly recognised and have resulted in significant research efforts during recent years. We suggest

that the mechanisms and short- and long-term consequences of the physiological stress response of the mother and fetus should be key elements of this research agenda. Important immediate questions include the determinants of the maternal HPAA response during pregnancy and their effects on the fetus, possible differences in the consequences of maternal stress between male and female fetuses, and the role of stress-related mechanisms in common specific maternal disorders such as pre-eclampsia and polycystic ovary syndrome. The long-term goal is to gain better understanding of what makes men and women different in the terms of stress and disease and to recognise instances when men and women benefit from different types of prevention of stress-related disease.

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