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REVIEW

Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge

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Summary Stress and stress-related health impairments are major problems in human life and elucidating the biological pathways linking stress and disease is of substantial importance. However, the identification of mechanisms underlying a dysregulation of major components of the stress response system is, particularly in humans, a very challenging task. Salivary cortisol responses to diverse acute challenge paradigms show large intra- and interindividual variability. In order to uncover mechanisms mediating stress-related disorders and to potentially develop new therapeutic strategies, an extensive phenotyping of HPA axis stress responses is essential. Such a research agenda depends on substantial knowledge of moderating and intervening variables that affect cortisol responses to different stressors and stimuli. The aim of this report is, therefore, to provide a comprehensive summary of important determinants of, in particular, human salivary cortisol responses to different kinds of laboratory stimuli including acute psychosocial stress as well as pharmacological provocation procedures. This overview demonstrates the role of age and gender, endogenous and exogenous sex steroid levels, pregnancy, lactation and breast-feeding, smoking, coffee and alcohol consumption as well as dietary energy supply in salivary cortisol responses to acute stress. Furthermore, it briefly summarizes current knowledge of the role of genetic factors and methodological issues in terms of habituation to repeated psychosocial stress exposures and time of testing as well as psychological factors, that have been shown to be associated with salivary cortisol responses like early life experiences, social factors, psychological interventions, personality as well as acute subjective-psychological stress responses and finally states of chronic stress and psychopathology.
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Contents

1. Introduction

A very prominent feature of stimulated salivary cortisol levels is the large variation in the response magnitude between individuals as well as across different situations or tests. Such variability can be observed with respect to the net cortisol output as well as the time course of hormone secretion after stress. Overall, the identification of mechanisms that determine the regulation and especially dysregulation of free cortisol responses to stress is, particularly in humans, a very challenging task. Since stress and stress-related health impairments have become major problems in human life, investigations into the biological pathways linking stress and disease are of major importance. An extensive phenotyping including salivary cortisol responsivity is essential in order to be able to uncover mechanisms mediating stress-related disorders and to potentially develop new therapeutic strategies in the future. Such a research agenda depends on substantial knowledge of moderating and intervening variables that affect free cortisol responses to different kinds of stressors and stimuli.

Besides naturally occurring acute and chronic stressors, acute cortisol responses can be stimulated in the laboratory by very different means including psychological stress protocols (e.g., cognitive tasks or public speaking paradigms like the Trier Social Stress Test (TSST)), a wide variety of pharmacological stimulants (e.g., administration of CRH, vasopressin or synthetic ACTH, etc.), intense physical exercise or even intake of standardized meals. Generally, for a research setting, laboratory stress protocols offer the advantage of standardization across test sessions but might lack the ecological validity of field studies or ambulatory assessments.

Laboratory psychological stress tasks have different potencies in their ability to reliably evoke salivary cortisol responses (Biondi and Picardi, 1999). In a meta-analysis covering 208 laboratory stress studies, Dickerson and Kemeny (2004) investigated conditions capable of eliciting HPA axis stress responses. They concluded that motivated performance tasks reliably elicited ACTH and cortisol responses if they were uncontrollable or characterized by social-evaluative threat. Tasks containing both elements were associated with the largest hormonal changes and the longest recovery times. More than 15 years ago, a psychosocial stress task was developed, which is characterized by both uncontrollable and social-evaluative elements. As it was developed in Trier, it was eventually named the Trier Social Stress Test. The TSST is a brief and highly standardized laboratory stress task consisting of a preparation period, a free speech and mental arithmetic task in front of an audience (Kirschbaum et al., 1993a) repeatedly showing cortisol responder rates of over 70% (Kudielka et al., 2007c,d).

While psychological stressors are central stimuli that require processing at higher brain levels, pharmacological challenges act at different levels of the HPA system and operate in a dose-dependent manner. For example, when assessing adrenal cortex functioning via release of cortisol from the adrenal cortex with an administration of a small dose of synthetic ACTH (e.g., 1 μg Synacthen) one would test for adrenal cortex sensitivity while administration of a larger dose (e.g., 250 μg Synacthen) would assess its maximum capacity (Daidoh et al., 1995). Many HPA axis stimulation tests trigger increases in cortisol via pharmacological stimulants acting primarily at the pituitary level, like exogenously administered CRH or vasopressin. When interpreting and comparing pharmacological provocation tests, researchers should be aware of the fact that study results are largely dependent on the applied stimulant and the chosen dosage. Generally, researchers applying pharmacological stimulants use very heterogeneous study approaches and designs and therefore yield very diverse results. For instance, in humans exogenously administered human CRH (hCRH) binds with high affinity to endogenous CRH-binding proteins which show low

affinity to ovine CRH (oCRH) (Sutton et al., 1995). Consequently, this results in very differential pharmacological effects. In the pharmacological testing of HPA axis regulation, reported outcome variables are typically ACTH and total plasma cortisol levels. Salivary cortisol concentrations are less frequently measured although the amount of salivary cortisol predominantly reflects the free, biologically active fraction of cortisol. Salivary cortisol agrees very well with the amount of free cortisol in blood but does not necessarily show high correlations with total cortisol levels (Vining et al., 1983; Kirschbaum and Hellhammer, 1989, 1994, 2007); note: compared to blood, absolute levels of cortisol are lower in saliva due to a relative abundance of the cortisol-metabolizing enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) converting active cortisol into inactive cortisone (Smith et al., 1996; van Uum et al., 2002). Further questions regarding analytical laboratory procedures are discussed by Gierens et al. (under revision).

Beside psychological stress tasks and pharmacological stimulation, intense physical exercise can elicit significant cortisol responses. Maximal exercise reaching the level of exhaustion leads to significant hormonal increases as well as sustained physical load exceeding 70% of the maximum oxygen uptake (VO_{2max}) (Luger et al., 1987; O'Connor and Corrigan, 1987; Kraemer et al., 1989; Wittert et al., 1991; Kirschbaum et al., 1992c). In contrast, short-term physical exercise with a lower workload appears to exert no or only minor cortisol responses (Friedmann and Kindermann, 1989; Kirschbaum et al., 1993b, 1994; Lovallo et al., 2006). However, significant plasma cortisol responses can be observed with a physical load between 60 and 65% VO_{2max} if maintained for hours (Deuster et al., 1992). In contrast to cortisol responses to psychological stress (see below), there seems to be no pronounced habituation effect in exercise-induced cortisol responses (O'Connor and Corrigan, 1987).

Finally, researchers should be aware of potential meal-related salivary cortisol increases (Gibson et al., 1999; Lovallo et al., 2006). Proteins have been primarily discussed as cortisol-stimulating agents (Slag et al., 1981; Anderson et al., 1987; Gibson et al., 1999; Benedict et al., 2005). Interestingly, standardized meals affect at least plasma cortisol levels differently according to time of day with higher meal-related increases at lunchtime (Brandenberger et al., 1982) compared to attenuated or even absent responses in the evening (Quigley and Yen, 1979; Follenius et al., 1982).

2. Determinants of salivary cortisol responses to challenge

The aim of this report is to provide an overview of important determinants of salivary cortisol responses to stress in humans demonstrating the role of age and gender, endogenous and exogenous sex steroid levels (e.g., the female menstrual cycle, use of oral contraceptives and hormone replacement therapy), pregnancy, lactation and breast-feeding, smoking, coffee and alcohol consumption as well as dietary energy supply in salivary cortisol responses to acute stress. Furthermore, we briefly summarize current knowledge of the role of genetic factors and methodological issues in terms of habituation to repeated psychosocial stress exposures and time of testing as well as psychological factors that have been shown to be associated with salivary cortisol responses like early life experiences, social support and social hierarchy, psychological interventions, personality factors as well as acute subjective-psychological stress responses and finally states of chronic stress and psychopathology. In view of the large number of potential sources of inter- and intraindividual response differences and the various laboratory challenge paradigms, we here necessarily review a selection of studies on human salivary cortisol responses to different types of challenges. Based on the available research on salivary cortisol, we mainly focus on responses to psychosocial laboratory stressors.

2.1. Age

In the last decades, several animal and human studies investigated whether aging affects the functioning of the HPA axis, for example, by exploring if age is related to a reduced resilience or less flexible functioning of this hormonal system (for a review and meta-analysis see Seeman and Robbins, 1994; Otte et al., 2005).

Surprisingly, still only very few studies are available reporting on salivary cortisol responses to psychological stress tasks. Nicolson et al. (1997) did not observe any age effects using a laboratory speech task, though task-related increases were very low. In accordance, we did not observe any age effects in salivary cortisol responses to psychosocial stress in healthy younger compared to older women (Kudielka et al., 1999). In men, we found no or only marginally higher responses in the older subjects (Kudielka et al., 2000; Rohleder et al., 2002). In a reanalysis of five independent studies from our laboratory with a total of 102 children, younger as well as older adults who were exposed to the Trier Social Stress Test (Kudielka et al., 2004a), we found elevated salivary cortisol responses in the group of elderly men (for sex difference see also below). Further very recent developmental studies indicate that salivary cortisol responses to psychological stressors in children and adolescents show age-related changes as discussed in another chapter of this issue (see Gunnar and Talge, in press).

In respect to pharmacological stimulation of the HPA axis with CRH with or without dexamethasone premedication or administration of CRH combined with vasopressin, the majority of studies showed elevated HPA axis responses in elderly men and women (Ohashi et al., 1986a; Pavlov et al., 1986; Dodt et al., 1991; Waltman et al., 1991; Greenspan et al., 1993; Heuser et al., 1994b; Born et al., 1995; Luisi et al., 1998; Vgontzas et al., 2001), including salivary cortisol responses (Kudielka et al., 1999). By administration of the 11β-hydroxylase-inhibitor metyrapone, the final enzymatic conversion into cortisol from its precursor molecule 11-deoxycortisol can be blocked in the adrenal cortex. Studies by Wilkinson et al. (1997) and Otte et al. (2003) point to a reduced glucocorticoid and mineralocorticoid feedback-sensitivity in older age after metyrapone treatment combined with a subsequent infusion of exogenous cortisol or the synthetic mineralocorticoid fludrocortisone. Direct stimulation of the adrenal cortex with synthetic or extracted ACTH does not point to a generally altered adrenal cortex capacity or sensitivity with progressive age (Kley et al., 1975; Parker et al., 1981, 2000; Vermeulen et al., 1982; Ohashi et al., 1986b; Roberts et al., 1990; Rasmuson et al., 1998; Martinez-Taboada et al., 2002). Only

in a very low dose ACTH-test (0.06 μg), Giordano et al. (2001) could observe a reduced adrenal cortex sensitivity in elderly subjects.

After physical exercise, cortisol levels remained unchanged or showed, in the main, comparable increases in younger and older men as well as women (Häkkinen and Pakarinen, 1995; Häkkinen et al., 1998; Kraemer et al., 1998, 1999; Traustadottir et al., 2004). However, these studies only report on total plasma cortisol but not salivary cortisol levels.

Age-related differences in HPA axis functioning are often explained by assumptions derived from the so-called glucocorticoid cascade hypothesis introduced by Sapolsky et al. (1986). This intriguing model, which was derived from numerous animal studies, proposes that age-related alterations in HPA axis regulation emerge due to a decrease in the ability of hippocampal neurons to maintain a sufficient negative feedback function. In view of contradicting evidence, De Kloet et al. (1991, 1998) formulated the corticosteroid receptor balance theory, proposing that even with older age homeostatic control could be maintained by a new balance between glucocorticoid and mineralocorticoid receptors, resulting in similar endocrine responses to stress in young and old subjects.

2.2. Gender and sex steroids

2.2.1. Gender, endogenuous sex steroids, menstrual cycle phase, oral contaceptives and corticosteroid binding globulin (CBG)

One of the most consistent findings employing psychological stress tasks (e.g., free speech, mental arithmetic, experimental harassment) is the significantly larger salivary cortisol response in healthy adult men compared to women following short-term laboratory stress (Steptoe et al., 1996; Nicolson et al., 1997; Earle et al., 1999; Seeman et al., 2001; Lovallo et al., 2006). Although pre-stress levels were not considerably different, we also repeatedly demonstrated that salivary cortisol responses to psychosocial stress differ between males and females applying the TSST (Kirschbaum et al., 1992c, 1995b; Kumsta et al., 2007b). Interestingly, salivary cortisol increases in men are up to twice as high as in women. The typical mean response magnitude in men ranges from 200 to 400% increase from baseline whereas in women 50—150% changes are usually found. Moreover, in men the sole anticipation of an upcoming psychosocial stress task led to a significant saliva cortisol response even when they were not actually confronted with the stressor. A similar anticipatory endocrine response was absent in women (Kirschbaum et al., 1992b). Meanwhile, we observed this sex difference in adrenocortical responsivity in more than a dozen studies (for reviews and meta-analysis see Kudielka and Kirschbaum, 2005; Otte et al., 2005; Kajantie and Phillips, 2006; Kudielka et al., 2007b).

In respect to the female menstrual cycle phase earlier studies only reported on plasma cortisol responses (Abplanalp et al., 1977; Tersman et al., 1991). In a follow-up study on sex differences in HPA axis responses to psychosocial stress, we investigated the role of the menstrual cycle phase applying the TSST in 81 men, women in the follicular phase of the menstrual cycle, women in the luteal phase, and women using oral contraceptives (Kirschbaum et al., 1999). While no sex differences emerged for total plasma cortisol, salivary cortisol responses differed significantly between groups. Women in the luteal phase had saliva cortisol stress responses comparable to those of men whereas women in the follicular phase or women taking oral contraceptives showed significantly lower salivary cortisol responses. Other studies replicated the findings of comparably high salivary cortisol stress responses in men and women during the luteal phase (Rohleder et al., 2001; Wolf et al., 2001) as well as higher salivary cortisol responses in women during the luteal phase versus women taking oral contraceptives (Rohleder et al., 2003). Such results underline the importance of strictly distinguishing between the total cortisol secretion and the levels of bioavailable free cortisol, as can be measured in saliva. These and earlier studies that also described blunted salivary cortisol stress responses in women taking oral contraceptives (Kirschbaum et al., 1995b, 1996a) raised the idea of a possibly modulating role of corticosteroid binding globulin since steroid binding globulin levels in the blood (including CBG) are significantly altered by intake of oral contraceptives containing the synthetic estradiol component ethinylestradiol (Moore et al., 1978; Wiegratz et al., 2003). Indeed, Kumsta et al. (2007a) could recently report on a significant negative correlation between CBG and salivary cortisol levels after TSST exposure in 115 women taking oral contraceptives while this correlation was not observed in the 93 medication-free men.

In respect to age, the same sex effect emerged for elderly subjects with men evincing higher salivary cortisol responses (Steptoe et al., 1996; Nicolson et al., 1997; Kudielka et al., 1998, 2004a). Although, we and others did not observe this sex effect in saliva cortisol responses in children after TSST exposure (Kudielka et al., 2004a) or in newborns undergoing discharge examinations (Gunnar et al., 1989), studies in newborns suggest that sex differences might be already present at birth. Male neonates had higher saliva cortisol responses when exposed to the standardized Brazelton neonatal behavior assessment (Davis and Emory, 1995), but girls showed a higher salivary cortisol response to heel prick as part of a standard pediatric examination (Buske-Kirschbaum et al., 2004). Unfortunately, several other stress protocols failed to elicit significant salivary cortisol increases in boys and girls (Hardie et al., 2002). It should finally be noted that other studies on heel stick blood draws, discharge examinations or infant inoculations also did not find sex differences in total plasma cortisol responses, supporting the finding that sex differences can not be reliably found in childhood (see Gunnar and Talge, in press).

Nevertheless, the possibility that different psychological stress protocols cause stressor-specific salivary cortisol responses should be acknowledged since some studies point to the potential importance of the gender relevance of psychological stressors. For example, Stroud et al. (2002) reported that men but not women had significant saliva cortisol increases after confrontation with an achievement challenge (mathematical and verbal tasks) whereas women but not men showed significant salivary cortisol responses to a social rejection challenge. Though, in the meta-analysis of Dickerson and Kemeny (2004) the importance of the two identified key stress-producing factors, namely uncontrollability and social evaluative-threat, was not modified by the sex of study participants.

Regarding pharmacological stimulation, CRH administration with and without dexamethasone premedication repeatedly resulted in higher total plasma cortisol responses in women compared to men (Greenspan et al., 1993; Heuser et al., 1994b; Born et al., 1995; Luisi et al., 1998; Künzel et al., 2003), though Kirschbaum et al. (1992c) did not observe any sex differences in a study measuring salivary cortisol responses after hCRH stimulation. A change in endogenous sex steroid levels due to ovariectomy in premenopausal women resulted in a slightly earlier but unchanged plasma cortisol peak after CRH injection (De Leo et al., 1998) while others reported on heightened basal urinary free cortisol levels and simultaneously reduced plasma cortisol responses to oCRH in estrogen-deficient young women with clinical amenorrhea (Biller et al., 1990). Salivary cortisol levels have not been reported in such studies. Likewise, in 102 healthy children, a maximal stimulation of the adrenal cortex with 250 μg synthetic ACTH did not render significant sex differences in total plasma cortisol responses across five different age cohorts (Lashansky et al., 1991). In the earlier mentioned study investigating the impact of sex, the female menstrual cycle phase and use of oral contraceptives (Kirschbaum et al., 1999), we also tested adrenal cortex capacity by injecting 250 μg synthetic ACTH. While no group differences emerged for total plasma cortisol, significant differences emerged for the salivary cortisol response to Synacthen. Women in the luteal phase of the menstrual cycle had the highest salivary cortisol responses followed by men, women in the follicular phase and users of oral contraceptives, respectively.

In response to physical exercise, the majority of studies did not reveal any sex differences in salivary as well as total plasma cortisol (Friedmann and Kindermann, 1989; Kraemer et al., 1989; Kirschbaum et al., 1992c). Finally, after a standardized meal, Lovallo et al. (2006) reported on higher saliva cortisol increases in women compared to men.

The described sex differences in HPA axis responses to stress may be due to sexual dimorphisms in brain structure and function (Patchev et al., 1995; Rhodes and Rubin, 1999; Cahill et al., 2001; Killgore and Yurgelun-Todd, 2001; Shors et al., 2001; Wang et al., 2007). Beside the impact of circulating CBG levels (Kirschbaum et al., 1999; Kumsta et al., 2007a), further prime candidates for explaining such observations are differences in the secretion of central arginine vasopressin (AVP) levels or circulating gonadal steroids with their complex effects on glucocorticoid and mineralocorticoid receptor regulation and functioning across men and women (for reviews and a meta-analysis see Kudielka and Kirschbaum, 2005; Otte et al., 2005; Kajantie and Phillips, 2006; Kudielka et al., 2007b).

2.2.2. Sex steroid supplementation and hormonal replacement therapy

Whereas many animal studies directly investigated the impact of estrogens on HPA axis regulation, only few experimental humans studies have been conducted with extremely rare reports on salivary cortisol responses.

In a placebo-controlled study, an 8-week estradiol supplementation in premenopausal women resulted in reduced plasma cortisol responses to mental arithmetic (Komesaroff et al., 1999) and Lindheim et al. (1992) reported a stress-induced HPA axis response before estradiol treatment but not after a 6-week sex hormone replacement in postmenopausal women. However, it cannot be ruled out that the latter 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 responses in a cross-over design, applying a relatively mild stressor. This result is in line with findings in an own study measuring salivary cortisol responses to stress. A 2-week estradiol treatment in postmenopausal women did not alter TSST-induced salivary cortisol responses, but HPA axis feedback regulation as measured by the combined Dex-CRH-test was increased in the estradiol-substituted postmenopausal women (Kudielka et al., 1999). Finally, Slayden et al. (1998) did not observe any changes in plasma cortisol responses before and after a 3-month treatment with estradiol in postmenopausal women applying an infusion with continuously increasing levels of synthetic ACTH after dexamethasone premedication. 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; Burleson et al., 1998).

In contrast, in healthy young men, the application of an estradiol-containing patch for 48 h resulted in elevated salivary cortisol responses to the TSST (Kirschbaum et al., 1996b). However, in estrogen supplemented hypogonadal men with a diagnosis of cancer, Komesaroff et al. (2002) reported attenuated total plasma cortisol responses to psychological stress while in male cancer patients treated with synthetic estrogens for at least 6 months no changes in plasma cortisol levels after dexamethasone treatment or in response to synthetic ACTH could be found (Schürmeyer et al., 1986).

Finally, to elucidate the impact of the sex hormone precursor dehydroepiandrosterone (DHEA), we conducted a placebo-controlled double blind study investigating HPA axis stress responses to the TSST in 75 men and women of advanced age after a 2-week DHEA or placebo treatment (Kudielka et al., 1998). While no differences emerged for salivary cortisol responses between the DHEA versus placebo treated group, DHEA-treated women showed ACTH stress responses similar to those of men but significantly enhanced compared to women after placebo treatment.

Data on the impact of androgens and progestins on HPA axis regulation in humans are extremely sparse and available results so far do not suggest a significant mediation of stress-related plasma or salivary cortisol responses (Lindheim et al., 1994; Burleson et al., 1998; Rohleder et al., 2002).

To conclude, it is obvious that the available data on the impact of sex steroid supplementation or hormonal replacement therapy in humans is very heterogeneous. Especially, studies applying a potent challenge to elicit cortisol responses in an experimental setting are still extremely scarce. Based on the existing evidence, we can at least conclude that even short-term sex steroid administration may modulate acute HPA axis stress responses as well as HPA axis feedback functioning.

2.3. Pregnancy, lactation and breast-feeding

Generally, pregnancy is accompanied by significant changes in HPA axis physiology characterized by marked increases in CRH, ACTH, plasma cortisol and CBG levels as well as

somewhat elevated free cortisol levels (McLean et al., 1995; Mastorakos and Ilias, 2003; de Weerth and Buitelaar, 2005; Lindsay and Nieman, 2005). Interestingly, salivary cortisol responses to the cold pressor test or hCRH challenge during pregnancy were found to be dampened (Schulte et al., 1990; Kammerer et al., 2002; for review see de Weerth and Buitelaar, 2005). It was hypothesized that this might be due to high circulating glucocorticoid or CRH levels since high concentrations could act by feedback mechanisms to blunt HPA axis responses to challenge, a desensitization of corticotrophic cells in the pituitary or, at least in part, the presence of CRH-binding proteins in maternal plasma that reduce the concentration of circulating potentially bioactive CRH. In animals, lactation has been associated with attenuated hormonal responses to different kinds of stressors (Carter and Altemus, 1997). It was therefore assumed that the human endocrine stress response might also be moderated by lactation in postpartum women. Indeed, after treadmill exercise, reduced plasma cortisol responses were found in lactating compared to non-lactating women (Altemus et al., 1995). Furthermore, suckling decreases basal levels of ACTH and total plasma cortisol in lactating women (Chiodera et al., 1991; Amico et al., 1994). Therefore, Heinrichs et al. (2001) investigated whether a blunting of endocrine stress responses in women can be ascribed to suckling as a short-term effect or to lactation in general. Thus, lactating mothers were randomly assigned either to breast-feed or to hold their infants before they were exposed to the TSST. While no significant differences in pre-stressor baseline hormone levels could be observed between groups, salivary and total plasma cortisol responses to stress were attenuated in breast-feeding women. From these data, it can be concluded that lactation in women, in contrast to rats, does not result in a general restraint of HPA axis responses to acute psychosocial stress. Rather, suckling seems to exert a short-term suppression of the cortisol response to psychosocial stress. In accordance with this finding others described comparable total plasma cortisol responses to psychosocial stress in lactating versus non-lactating women (Altemus et al., 2001; Redwine et al., 2001). Finally, a recent study raised the hypothesis that only multiple repeats of the pregnancy/lactation period might modulate HPA axis functioning since breast-feeding was associated with reduced salivary cortisol stress responsiveness among multiparous but not primiparous mothers (Tu et al., 2006). A comprehensive review on lactation and stress and the protective effects of breast-feeding in humans can be found in Heinrichs et al. (2002), providing a detailed discussion of the potential inhibitory impact of the lactogenic peptides oxytocin and prolactin on different levels of HPA axis regulation.

2.4. Nicotine, coffee, alcohol and dietary energy supplies

Nicotine is a potent acute stimulator of the HPA axis through induction of CRH release after binding to cholinergic receptors in the locus coeruleus and hypothalamus (for reviews see Fuxe et al., 1989; Weidenfeld et al., 1989; Matta et al., 1998; Rosecrans and Karin, 1998). After smoking at least two cigarettes, smokers show significant elevations of salivary cortisol levels (Kirschbaum et al., 1992d, 1994, 1997). Regular consumption of nicotine could therefore lead to chronically elevated ACTH and/or cortisol levels with reduced responsiveness of the HPA axis to acute challenge. In fact, habitual smoking changes the HPA axis responses to stress; blunted salivary cortisol responses to the TSST have been repeatedly observed in habitual smokers compared to non-smokers (Kirschbaum et al., 1993b, 1994; al'Absi et al., 2003) while nicotine abstinence did not alter salivary cortisol responses to psychosocial stress in smokers (al'Absi et al., 2002, 2003). Interestingly, significant differences in adrenocortical responses between smokers and non-smokers have been reported only after stimulation at a supra-pituitary level. Injections of hCRH or bicycle ergometry resulted in no or only marginally blunted salivary cortisol responses in chronic smokers versus non-smokers (Kirschbaum et al., 1993b, 1994). In the Dex-CRH-test, only ACTH responses showed positive associations with nicotine consumption (Künzel et al., 2003). In sum, acute as well as habitual smoking is a potential intervening variable which potentially accounts for some of the inter- and intraindividual variation observed in salivary cortisol responses to challenge (for review see Rohleder and Kirschbaum, 2006).

Beside nicotine, it has been shown that caffeine intake can potentially activate important components of the pituitary-adrenocortical response in humans during resting states leading to increased plasma as well as salivary cortisol levels (Lovallo et al., 1996, 2005). However, this finding is not unequivocal since others did not observe increases in neither basal free nor total cortisol levels after consumption of coffee or tea (Quinlan et al., 1997; Lane et al., 2002; Lovallo et al., 2006; Tsubouchi et al., 2006; MacKenzie et al., 2007; Steptoe et al., 2007). In stress experiments evidence has emerged for combined stimulatory effects of caffeine and physical exercise or psychological stress in form of mental arithmetic, a reaction time task or an academic exam on plasma and salivary cortisol responses (Lane et al., 1990; al'Absi et al., 1995, 1998; Shepard et al., 2000; Lovallo et al., 2006). Finally, caffeine consumption was not related to HPA axis responses applying a Dex-CRH-test, though salivary cortisol levels have not been reported here (Künzel et al., 2003).

There are several reports suggesting that chronic alcohol consumption impacts on basal HPA axis activity as well as HPA axis reactivity to stress (Gianoulakis et al., 2003; Adinoff et al., 2005). Lovallo et al. (2000) observed blunted salivary cortisol responses to a public speaking challenge in alcohol-dependent patients compared to healthy controls, but others could not find HPA axis response differences to the TSST comparing alcoholics or abstinent alcohol-dependent subjects with non-alcoholics (Munro et al., 2005; McRae et al., 2006). Consistently, in pharmacological stimulation tests, reduced HPA axis responses to stimulation with hCRH and Synacthen were repeatedly observed in chronic alcoholics compared to non-alcoholics (Heuser et al., 1988; Costa et al., 1996; Kearney et al., 2000; for review see Adinoff et al., 2005). Also subjects with a positive family history of alcohol-dependence repeatedly showed lower stress-induced plasma and salivary cortisol responses and an alcoholic drink blunted subsequent stress-induced increases in plasma ACTH and cortisol (Dai et al., 2002, 2007; Sorocco et al., 2006). However, findings are again not unanimous. Zimmermann et al. (2004) reported on elevated HPA axis stress response

to the TSST and a stronger dampening by alcohol in sons of alcoholic fathers compared to control subjects. Such a heightened plasma cortisol response to a psychosocial stressor was also described by Uhart et al. (2006) in Caucasian but not African-American men and women with a positive family history of alcoholism. In sum, chronic alcohol consumption, a positive familiy history of alcohol dependence as well as acute ethanol intake should be considered as potential factors impacting on salivary cortisol responses to acute stress.

Finally, the availability of dietary energy supplies appears to exert important regulatory functions in pituitary-adrenal stress responses pointing to an important role of the nutritional state. In a first study, the effects of short-term fasting and subsequent glucose administration on the salivary cortisol response to the TSST were investigated (Kirschbaum et al., 1997). Although glucose load per se did not affect saliva cortisol levels, the stress exposure induced a large salivary cortisol response in glucose-treated subjects. In contrast, fasted subjects who received tap water did not respond to the psychological stressor with significant changes in salivary cortisol levels. The finding that low glucose levels appear to inhibit adrenocortical responsiveness in healthy subjects was rather surprising. In a second study, subjects either received glucose, protein, fat, or water 1 h before TSST exposure (Gonzalez-Bono et al., 2002). Absolute saliva cortisol levels and net increases were greater in the glucose group in comparison to the other three groups and the salivary cortisol response was positively correlated with changes in blood glucose. In sum, it can be assumed that a central mechanism may be responsible for regulation of energy balance and HPA axis activation rather than peripheral mechanisms. These studies show that blood glucose levels should be standardized when studying salivary cortisol responses. This could be achieved by standardization of the nutritional state before onset of an experiment, e.g. by the consumption of a standardized meal or the administration of a glucose-containing standard beverage at the beginning of a stress experiment. Recently, Rohleder and Kirschbaum (2007) reviewed the effects of neuropeptides involved in energy homeostasis and appetite regulation and concluded that current evidence insufficiently explains the observed negative HPA axis modulation by low glucose levels since orexigenic peptides stimulate the HPA axis rather than suppressing it. Lastly, researchers should also be aware of potential alterations of salivary cortisol responses to acute laboratory stress due to intake of vitamin compounds (Brody et al., 2002).

2.5. Genetic factors

Salivary cortisol responses to acute challenge are significantly influenced by genetic factors as shown in twin studies as well as in candidate gene studies on polymorphisms in HPA axis related genes, coding for example for the glucocorticoid, mineralocorticoid or melanocortin 2 (ACTH) receptors (for a review see Wüst et al., 2004a). In a first pilot study, the heritability of salivary cortisol responses was investigated in a rather small and heterogeneous sample of monozygotic (MZ) and dizygotic (DZ) twins who were exposed to the TSST, an injection of 100 μg hCRH and exhausting physical exercise (Kirschbaum et al., 1992b). While the results suggested a substantial heritability of salivary cortisol peak levels after hCRH administration, salivary cortisol responses to the TSST showed only a trend towards heritability and no indication for an impact of genetic factors was detectable for responses to bicycle ergometry. In a larger sample of young healthy male twin pairs (33 MZ and 25 DZ) the TSST was performed three times in 1-week intervals (Federenko et al., 2004). In accordance with the hypothesis that "trait"-like components of the endocrine stress response may become more apparent with repeated stress exposures, it was shown that the genetic influence on HPA axis reactivity was low at the first TSST stress exposure, but increased substantially with the repetition of the same stress protocol. This strongly supports the notion that genetic factors do contribute to the variability in salivary cortisol responses to psychosocial stress. While also a significant heritability of salivary cortisol increases to 250 μg synthetic ACTH (Synacthen) was found in this sample, surprisingly no clear indication for a genetic effect on responses to 1 μg Synacthen was found (Federenko, 2003).

More recently, in a series of studies Wüst and coworkers investigated for the first time whether variants of the glucocorticoid or mineralocorticoid receptor gene might contribute to the large interindividual variability of HPA axis stress reactivity and amongst others they documented a sex-specific association between different GR gene polymorphisms and salivary cortisol responses to acute psychosocial stress (Wüst et al., 2004b; DeRijk et al., 2006; Kumsta et al., 2007b).

2.6. Methodological factors: habituation and time of testing

From a methodological point of view, researchers should be aware of the fact that a rapid habituation of a salivary cortisol response after repeated exposure to (initially) stressful situations emerges in various psychological stress protocols (Gunnar et al., 1989; Deinzer et al., 1997; Pruessner et al., 1997; Schommer et al., 2003; Federenko et al., 2004; Kudielka et al., 2006b). It has been hypothesized that such habituation may be ascribed to a reduction in context variables across stress sessions. Wüst et al. (2005b) could recently document a substantial interindividual variability of salivary cortisol response habituation patterns. While 52% of the participants showed the well-known response habituation to the TSST, almost 16% showed a response sensitization across three test sessions. Interestingly, such habituation effects appear to be rather specific for HPA axis responses since parameters of the sympathetic nervous system, the immune system, blood coagulation system and indices of hemoconcentration showed rather uniform activation patterns with repeated exposure to psychosocial challenge (Schommer et al., 2003; von Känel et al., 2004, 2006; Mischler et al., 2005).

Another methodological issue relates to the time of testing. Firstly, in case of early morning sessions, an experimenter should ensure that the onset of a stress experiment does not interfere with the cortisol awakening response (CAR). Secondly, we observed that absolute salivary cortisol response curves after acute psychosocial stress exposure are much higher in the morning although comparable net free cortisol increases can be assessed with equal reliability in the morning and afternoon (Kudielka et al., 2004b). Interestingly, such effects did not emerge for ACTH or total plasma cortisol. Numerous studies investigated the effect of time of day on

HPA axis responses applying different provocation tests. The majority of these studies conclude that maximum plasma cortisol increases can be achieved in the afternoon; however, salivary cortisol responses have not been measured in such studies (for an overview see Kudielka et al., 2004b). After physical exercise salivary cortisol responses appear not to show a significant effect depending on time of day (Thuma et al., 1995; Dimitriou et al., 2002). While one study reported a greater rise in total cortisol in the evening than in the morning, comparable increases emerged for salivary cortisol.

2.7. Early life experiences: pre- and postnatal stress

There is first evidence that stressful pre- and postnatal life experiences potentially exert a lifelong impact on HPA axis responses to diverse psychological and pharmacological challenge paradigms (Huizink et al., 2004; Luecken and Lemery, 2004; Weinstock, 2005; Luecken and Appelhans, 2006; Entringer et al., in press). Fetal programming of the HPA axis is proposed as one key mechanism underlying the link between prenatal stress, adverse birth outcomes (particularly low birth weight) and an enhanced vulnerability for several diseases later in adult life. Indeed, birth weight was inversely related to salivary cortisol responses to acute psychosocial stress in male adults and boys (Wüst et al., 2005a; Jones et al., 2006). Salivary and plasma cortisol responses to pharmacological stimulation have also been shown to be significantly associated with birth weight and gestational age (Kajantie et al., 2003; Ward et al., 2004). Furthermore, a study on the effects of high familial adversity in early childhood on salivary cortisol stress responses to unfamiliar situations suggests a significant gene-environment interaction (Ouellet-Morin et al., 2008). Finally, recent studies reported minor but significant relations between childhood attachment styles and salivary cortisol responses to acute stress during adulthood (Luecken, 1998, 2000; Quirin et al., 2008) or between adult couple attachment styles and salivary cortisol responses in relationship conflict situations (Powers et al., 2006). Other studies point to significant interactional effects of psychiatric symptoms in adult life and childhood trauma on HPA axis responses to psychological stress and pharmacological stimulation assessed during adulthood (Heim et al., 2000, 2008), though salivary cortisol responses have not been reported in these studies.

2.8. Social support, social hierarchy and psychological interventions

It is known that the social environment can exert modulating effects on salivary cortisol stress responses. In men, brief social support resulted in significantly decreased salivary cortisol responses depending on the quality of support whereas women showed even marginally higher salivary cortisol responses when supported by their own partner in life (Kirschbaum et al., 1995a). Heinrichs et al. (2003) observed that the neuropeptide oxytocin enhances the buffering effect of social support on salivary cortisol stress responsiveness in men pointing to a potential underlying biological mechanism for stress-protective effects of positive social support. Also the position in the social hierarchy seems to be relevant for acute salivary cortisol responses to acute stress. In a sample of 63 army recruits, socially dominant subjects showed high salivary cortisol increases compared to only modest elevations in subordinate men after TSST exposure and physical exercise (Hellhammer et al., 1997). Besides the social environment, psychological interventions like brief group-based cognitive-behavioral stress management or relaxing music potentially reduce salivary cortisol stress responses to an acute stress exposure and such effects may persist over time in both men and women (Gaab et al., 2003; Khalfa et al., 2003; Hammerfald et al., 2006).

2.9. Personality factors

It is tempting to speculate that salivary cortisol responses to stress are influenced, at least in part, by stable trait factors since the endocrine response to psychosocial stress can be viewed as a close interaction between situation and person variables within a given context. However, in most studies no close relationship between personality factors and stress-induced saliva cortisol increases could be observed. Though, associations between personality traits and salivary cortisol stress responses emerge after repeated stress exposures (Kirschbaum et al., 1992a, 1995c; Pruessner et al., 1997). While novelty may mask the impact of personality on the salivary cortisol stress response on the first exposure, differences in the ability to cope with the stressful situation may lead to different cortisol stress response patterns on subsequent stress exposures. Thus repeated stress exposures and data aggregation seems to enhance the likelihood to find stable and meaningful associations between personality variables and salivary cortisol stress responses.

2.10. Acute subjective-psychological stress responses

In humans, acute stress triggers multiple psychological as well as physiological responses. Since such different responses to a stressful event theoretically represent indicators of the same construct, a strong association between acute psychological and physiological responses, i.e. a high psychoendocrine covariance, should be expected. However, so far analyses of psychoendocrine covariance have produced inconsistent and largely inconclusive results (for review see Schlotz et al., 2008). Such inconsistencies might reflect imperfect coupling of the different stress response systems. Applying an innovative approach, Schlotz et al. (2008) showed that earlier inconsistent findings are probably, at least in part, based on the different dynamics of these systems. While acute subjective psychological stress responses occur within seconds and may change dynamically during a prolonged stress situation, cortisol responses reach their peak approximately 15—20 min after the onset of the stressor and change less dynamically. According to the hypothesis that associations between an acute psychological and endocrine stress response should be higher when response correlations are computed at similar system-specific stages relative to the onset of the stressor, the authors found that subjective-psychological responses precede HPA axis responses and that high levels of cortisol are associated with lower later levels of anxiety and activation using a cross-correlational analytic approach. In sum, Schlotz and

coworkers demonstrated for the first time that time-lagged cross-correlations need to be tested if one wants to draw valid conclusions about psychoendocrine covariance in response to different stressors in humans.

2.11. Chronic stress, burnout and vital exhaustion

The question whether an HPA axis hyper- or hyporesponsivity to acute stress may occur when an individual is chronically stressed or exhausted and no longer able to cope with environmental stress is still open to debate. The few studies that applied psychological stressors or even more seldom pharmacological stimulation procedures potentially point at a subtle free cortisol hyporeactivity in participants with higher levels of chronic stress, burnout and exhaustion. However, results are extremely heterogeneous with reports on blunted as well as heightened free cortisol responses or no differences in the HPA axis response to a single stress exposure (for reviews see Kudielka et al., 2006a; Melamed et al., 2006). It can only be speculated why the picture of results is relatively heterogeneous. Inconsistencies between studies can probably be, at least in part, ascribed to methodological aspects (e.g., the use of different psychometric scales and diagnostic criteria) as well as large differences in the control of confounding or intervening factors of HPA axis regulation. For instance, only some studies controlled for psychological factors that might have influenced self-report, like negative affectivity, depression or anxiety. It was also hypothesized that chronic stress may first lead to hyperactive HPA axis functioning, while the system turns to hypoactive functioning when a state of exhaustion is reached and the individual is no longer able to cope with environmental stress (for review see Kudielka et al., 2006a). Interestingly, under repeated psychosocial short-term stress, an association between vital exhaustion and salivary cortisol responses emerged (Kudielka et al., 2006b). Linear regression revealed a negative dose—response relationship between exhaustion and the degree of response habituation to three TSST exposures. With this, it can be assumed that situational or psychological factors initially mask an existing impact of exhaustion since an effect of exhaustion became only apparent after repeated stress exposures.

2.12. Clinical studies and medication intake

It is well-known that HPA axis responses (including salivary cortisol increases) to acute psychosocial stress as well as different pharmacological stimulation tests are significantly altered in several clinical populations ranging from psychiatric diseases to somatic complaints. To date, the TSST has been applied in patients suffering from major depression, anxiety disorder, social phobia, posttraumatic stress disorder, attention deficit hyperactivity disorder, chronic fatigue syndrome, fibromyalgia, diverse pain disorders, functional gastrointestinal disorders, diabetes, different manifestations of chronic atopy, atopic dermatitis or chronic allergic asthma, and breast cancer survivors, to give some examples. A detailed description of these results is surely beyond the scope of this overview and numerous reviews on this topic can be found elsewhere (Holsboer, 1989; Heuser et al., 1994a; Tsigos and Chrousos, 1994, 2002; Buske-Kirschbaum et al., 2001; Buske-Kirschbaum and Hellhammer, 2003; Burke et al., 2005; Kudielka et al., 2007c; Jessop and Turner-Cobb, 2008). Irrespective of the heterogeneity of findings and evident methodological differences across studies, results show that differences between patients and healthy controls are more likely observed when the system is challenged.

Finally, researchers should be aware of the fact that even short-term medication (e.g., with glucocorticoids, psychoactive drugs, or other pharmaceuticals ingested for preventive reasons) potentially alters salivary cortisol responses to psychosocial stress or pharmacological stimulation in patients as well as healthy controls although free cortisol baseline levels might remain unchanged (Tunn et al., 1992; Makatsori et al., 2004; Pariante et al., 2004; Maheu et al., 2005; Fries et al., 2006; Kudielka et al., 2007a). Likewise, treatment with different antidepressants significantly alters HPA axis responses to Dex-CRH as shown in several studies, though free cortisol responses have not been measured in such studies (Künzel et al., 2003; Rinne et al., 2003; Schüle et al., 2003; Nikisch et al., 2005). Further in-depth discussion about underlying mechanisms how such medication impacts on HPA axis stress regulation can be found elsewhere (Barden et al., 1995; Holsboer and Barden, 1996; Holsboer, 2000; Pariante and Miller, 2001).

3. Final remarks

The HPA axis is a vital part of the human stress response system. Therefore, understanding determinants of inter- and intraindividual variability in cortisol regulation as well as mechanisms underlying pathologically relevant dysregulation of cortisol activity is a key topic in psychobiological stress research. Evidence from research over the last decades clearly documents that salivary cortisol is a useful and valid biomarker in stress research (see Hellhammer et al., in press). Amongst other insights, we meanwhile know that numerous moderating and intervening factors, carefully described in different laboratories and summarized in the present paper, can have an impact on cortisol responses. This is certainly a somewhat challenging situation as it is not possible to control for countless potential confounders in each study and this holds particularly true when sample sizes are relatively modest. This is the rule rather than the exception in our field. However, it first should be noted that most of these factors do not specifically modulate salivary cortisol but also cortisol levels in blood. In general, the experience that the visible complexity of a system increases with proceeding insight into the system is a rather familiar experience for many research disciplines. Moreover, the awareness of modulators certainly offers the opportunity to reliably detect effects and to improve, technically spoken, the signal to noise ratio. This is crucial as the effects that can be expected in psychobiological stress research are usually of modest size (although they can well be of psychobiological or clinical relevance).

Thus, our knowledge might be helpful at different stages of a research project. First, when planning an experiment, it might guide the researchers' decision on exclusion criteria, eligibility and selection of subjects (depending on the study question), further information that should preferably be provided by participants (e.g., assessed in accompanying demographic or psychometric assessments), factors that

could be held constant across subjects, and issues that are relevant for the instruction of subjects before and during the assessment period (e.g., subjects' coffee consumption at test days). For example, smoking or the intake of oral contraceptives can be defined as exclusion criteria, can be held constant across different study groups, can afterwards be used as covariate, or defined as the experimental manipulation in a (quasi-) experimental study design. Such decisions consequently impact on the theoretically optimal sample size of a study, apart from considerations of feasibility. If possible, the sample size should be based on a priori calculations (e.g., with the software "GPower3" by Faul et al., 2007, which is freely accessible at http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3). Due to the large variability of possible research questions and study designs, it is difficult to give specific recommendations. However, we think that at least two factors should be considered in the vast majority of studies which include the assessment of cortisol responses to challenge. The first one is the time of day when the subjects are exposed to the challenge and in most studies it should be doable to hold this variable relatively constant. The most convenient time window is the late afternoon. The second prime variable is the subjects' sex. It is often tempting to restrict the sample to males (as it is done in most rodent studies in our area) and this is surely an acceptable approach to control for this factor. However, given the increasing awareness of the striking quantity of sex-related influences on brain function and disease vulnerability (for a recent review see Cahill, 2006) males and females should be included whenever possible. The gold standard to account for the potential impact of the menstrual cycle on salivary cortisol responses in women is to assess the subject's cycle phase and to study women in the follicular and women in the luteal phase (repeated measures or group design depending on the study). Focusing on only one menstrual cycle phase or studying only women using oral contraceptives (OC) are less laborious alternatives but both approaches result in a limited generalizability of findings. It could be argued that particularly OC intake is a clear artificial state and should thus be a general exclusion criterion. However, in many countries the majority of (young) women use OCs. Thus, investigating female cortisol responses in front of the background of widespread OC usage is — to a certain degree — a research question in its own right. In this respect, it is also obvious that we need to consider a female's pubertal or menopause status, respectively.

Second, when it comes to data analysis, knowledge about moderating and intervening factors can help to select (or test) a set of potentially (or the most) relevant control variables to be used as covariates in statistical models. However, researchers should be aware of the fact that the appropriate number of covariates depends on the sample size since model overfitting might lead to spurious results (Babyak, 2004). In general, the larger the available sample size, the more variables can be added to a respective model.

Third, the acknowledgement of potential sources of variance is finally essential when it comes to data interpretation. This might be especially important, for example, for studies based on small sample sizes, quasi-experimental designs, studies with limitations in randomization, or studies conducted under ambulatory settings and field conditions, etc. A discussion of potential sources of variance might contribute to the explanation of contradictory or conflicting results across different studies and might trigger the exploration of further yet unknown sources of variance. Another important aspect is the issue of generalizability of given results. For example, if a study examines exclusively middle-aged adult men in order to eliminate any impact of age and gender, the results might not apply to females or other age cohorts, resulting in reduced generalizability (see above). Finally, in case of secondary analyses and reanalyses that take advantage of preexisting samples or data sets, researchers should be particularly aware of potential sources of inter- as well as intraindividual variance since a given sample might have very special characteristics due to the original study aim participants were recruited for. However, we should also bear in mind that even in highly controlled studies results might be sample-specific for unknown reasons. Therefore, replications in diverse study samples are always a necessary requirement.

Meanwhile, clinical studies continue to accumulate evidence that different diseases are associated with characteristic salivary cortisol stress response profiles. Furthermore, biological mechanisms begin to unfold which could be helpful in explaining stress-disease associations. Finally, the question how HPA axis challenge paradigms that are capable to elicit acute salivary cortisol responses (including psychosocial stress protocols like the Trier Social Stress Test) can be applied as a diagnostic tool for the prediction of disease susceptibility and symptom severity and/or for monitoring the efficacy of interventions still remains an important area of research for the future.

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Conflict of interest

This work was carried out while all authors were affiliated with the Graduate School of Psychobiology, Department of Theoretical and Clinical Psychobiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany.

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