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Persistent effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects—A randomized controlled trial

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Summary Psychosocial stress leads to a release of cortisol. While this psychoneuroendocrine response helps to maintain physiological as well as psychological equilibrium under stress, exaggerated secretion of cortisol has been shown to have negative effects on somatic health and cognitive functioning. The study set out to examine the long-term effects of cognitive-behavioral stress management training on cortisol stress responses in healthy men and women.

Eighty-three healthy subjects were randomly assigned to cognitive-behavioral stress management (CBSM) training or a control condition. Four months after the CBSM, 76 subjects underwent a standardized psychosocial stress test. Salivary cortisol responses were assessed repeatedly before and after the stress test.

Subjects in the CBSM group showed significantly reduced cortisol stress responses. With regard to gender, this effect was observed in both men and women. However, the magnitude of the CBSM effect on cortisol responses was smaller in women than in men. Use of oral contraceptives in women influenced the cortisol response, but did not have an impact on the CBSM effect on cortisol.

The results show that the previously reported attenuation of cortisol stress responses through CBSM persists and are observable in both men and women. Since stress-induced alterations of hypothalamus pituitary adrenal axis functioning are discussed to be involved in the onset and maintenance of both somatic and psychiatric conditions, similar interventions could be used for prevention and therapy of these detrimental stress effects.

1. Introduction

In terms of its ubiquitous effects on important physiological systems, the hypothalamus–pituitary–adrenal (HPA) axis has been proposed as a major

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pathway linking psychosocial stress to its negative consequences on somatic and psychological well being (McEwen, 1998). There is accumulating evidence supporting a causal relation between increased activity and reactivity of HPA axis hormones and negative health outcomes.

For example, acute HPA axis responses to laboratory stressors have been shown to be linked to the risk for upper respiratory tract infection that is associated with stressors in the natural environment (Cohen et al., 2002). With respect to possible long-term effects, an abnormal cortisol pattern was shown to be prospectively associated with increased incidence of cardiovascular-related events and type 2 diabetes in men (Rosmond et al., 2003). Furthermore, results from the 'MacArthur studies of successful aging' provide evidence for long-term detrimental effects of elevated cortisol levels in the elderly, with higher baseline urinary free cortisol levels being related to declines in memory performance in women (Seeman et al., 1997) or higher incidence of fractures in men and women (Greendale et al., 1999).

In addition, cortisol is a primary mediator of allostatic load (representing the cumulative physiological burden exacted on the body through attempts to adapt to life's demands), which has been associated with significantly increased risk for 7-year mortality as well as declines in cognitive and physical functioning in the elderly (Seeman et al., 2001). Also, administration of cortisol before retrieval leads to a decrease in memory performance (Het et al., 2005).

The release of cortisol has been shown to be related to the experience or anticipation of stress (Smyth et al., 1998; Dickerson and Kemeny, 2004; Gaab et al., 2005). Therefore, interventions aiming to modulate the perception and appraisal as well as to improve stress-related coping strategies are possible means with which to modulate cortisol levels as a consequence of stressful experiences. In a randomized controlled trial study, our group reported attenuated cortisol responses to a standardized psychosocial stress test in healthy male subjects two weeks after a short, group-based cognitive-behavioral stress management training (CBSM) (Gaab et al., 2003). The current study set out to examine the stability over time and the generalizability with regard to gender of these endocrine effects of CBSM in healthy subjects.

2. Methods

2.1. Subjects and design

Three hundred and fifteen subjects (all 2nd-year psychology students of the University of Zurich in 2002) were invited to participate in the study through a letter to all 2nd-year psychology students of the University of Zurich. Recruitment was restricted to this population to reduce interindividual differences in the frequencies and extent of external academic stressors. Interested subjects had the opportunity to enroll online. They then received a screening questionnaire, containing exclusion criteria (any acute or chronic somatic or psychiatric disorder) and a complete description of the study. One hundred and two students enrolled online and 96 returned the screening questionnaire. Thirteen interested subjects had to be excluded, and 83 subjects, therefore participated in the study.

Upon return of all screening questionnaires and informed consent, all subjects fulfilling the selection criteria were randomly assigned to eight groups (four treatment and four control groups). In order to allow CBSM group sessions, group size was restricted to maximum $N=12$. Allocation concealment was achieved through the use of sequentially numbered, opaque and sealed envelopes. Randomization resulted in eight groups (four CBSM groups: $N=42$, four control groups: $N=41$; with 10 or 11 subjects in each group). Since treatment groups 1–4 and waiting control groups 5–8 did not differ significantly in terms of demographic variables (age, gender, habitual smoking, use of oral contraceptives and body mass index, data not shown), they were joined to form one treatment group and one control group. Subjects in the treatment and control group did not differ significantly with regard to the distribution of gender, smoking and use of oral contraceptives (see Table 1).

Four months after the termination of the CBSM for the treatment group, all subjects underwent a standardized psychosocial stress test (Trier Social Stress Test, TSST, Kirschbaum et al., 1993). Subjects of the CBSM group performed the TSST within a 2-week period, whereas controls performed the TSST in a 4-week period. To rule out major differences of external factors, such as

Table 1 Demographic variables.

	CBSM group	Control group	
Gender (male/female)	11/31	13/28	$\chi^2=0.31$; $P=0.58$
Smoking (yes/no)	13/29	6/35	$\chi^2=3.13$; $P=0.08$
Oral contraceptives (yes/no)	17/14	12/15	$\chi^2=0.62$; $P=0.43$

season and external stressors, all subjects performed the TSST with the same four weeks. Not all participants underwent the TSST. Reasons for dropout were: Refusal to further participate in the study ($N=1$) and inability to keep the TSST appointment within the TSST testing period ($N=6$). Subjects not performing the TSST did not differ in baseline variables from TSST performers (age, gender, habitual smoking, use of oral contraceptives and body mass index, data not shown). Thirty-nine subjects of the CBSM and 37 subjects of the control group performed the TSST. After the termination of the study, all controls received CBSM training.

2.2. Psychosocial stress test

The Trier Social Stress Test (TSST) has repeatedly been found to induce profound endocrine responses in 70–80% of the subjects tested (Kirschbaum et al., 1993). Subjects were briefly introduced to the TSST (2 min) and then returned to a different room, where they had 10 min to prepare and to complete a questionnaire designed to assess cognitive appraisal processes (PASA) of the anticipated stress situation. Afterwards, subjects were taken back into the TSST room, where they underwent a simulated job interview (5 min) followed by a mental arithmetic task (5 min) in front of a committee of two people. Saliva samples were obtained immediately before, and one, 10, 20, 30, 45, and 60 min after the TSST. To control for variations of cortisol levels over the circadian rhythm, the TSST was performed from 14.00 to 18.00 h. The TSST committee and the study personnel were blind to group assignment. The TSST was performed in different rooms than the CBSM.

2.3. Psychometric measures

Anticipatory cognitive appraisal processes in the TSST were assessed with the Primary Appraisal Secondary Appraisal Scale (PASA). The PASA comprises 16 situation-specific items, forming four primary (Challenge, Threat, Self-Concept of Own Competence and Control Expectancy) and two secondary scales (Primary Appraisal = (Challenge + Threat)/2 and Secondary Appraisal = (Self-Concept of Own Competence + Control Expectancy)/2). Primary scales can be summed up to a general stress index (Stress Index = (Primary Appraisal − Secondary Appraisal), representing the sum of primary and secondary appraisal. The reliability and factorial validity of the PASA has been shown to be good (Gaab et al., 2005).

2.4. Cognitive-behavioral stress management (CBSM)

All subjects attended group-based cognitive-behavioral stress management training described elsewhere (Gaab et al., 2003). Groups met on two alternate Saturdays or Sundays, respectively. Groups of up to 11 subjects received a total of 10 h of CBSM. The sessions were conducted by two clinical psychologists (JG and KH), according to a standardized training manual. The CBSM focused on four cognitive-behavioral stress-reducing techniques (cognitive restructuring, problem-solving, self-instruction, progressive muscle relaxation). All participants received a training manual containing a summary of theoretical models and stress-reducing techniques as well as a set of flash cards (size: 10 × 7 cm), which briefly described each CBSM technique. Exercises and role-plays used in the group therapy sessions did not resemble the situation used in the TSST. The CBSM training employed was similar to the training used in an earlier publication (Gaab et al., 2003).

2.5. Sampling methods and biochemical analyses

Saliva was collected with Salivette (Sarstedt, Rommelsdorf, Germany) collection devices. Samples were stored at −20 °C until biochemical analysis took place. Salivary free cortisol was analyzed by using a commercial chemiluminescence immunoassay (IBL Hamburg, Germany). Inter- and intraassay coefficients of variation were below 10%. To reduce error variance caused by imprecision of the intraassay, all samples of one subject were analyzed in the same run.

2.6. Statistical analyses

Repeated measures ANOVAs and ANCOVAs tested for significant condition × time interactions on salivary cortisol responses. All reported results were corrected by the Greenhouse-Geisser procedure, where appropriate (violation of sphericity assumption). Pairwise comparisons were performed for each cortisol sample. For cortisol parameters, areas under the response curve were calculated with respect to increase from increase (AUCi) using the trapezoidal method as an indicator for the integrated cortisol response in the TSST (Pruessner et al., 2003). In line with previous observations

(Gaab et al., 2003), we expected a multivariate effect size of $f^2=0.20$ (representing a medium to large effect size). Based on 0.8 power to detect a significant difference of this effect size and a 5% significance level, 80 subjects were required. Unless indicated, all results shown are means ± standard error of means (SEM). When appropriate, effect size parameters are shown (effect size conventions: f^2: 0.02 = small, 0.15 = medium, 0.35 = large; d: 0.20 = small, 0.50 = medium, 0.80 = large).

3. Results

The TSST resulted in a significant cortisol stress response in all subjects (time effect: $F(2.85/210.50)=44.83$; $P<0.001$). Groups did not differ in their baseline cortisol levels (group effect at baseline: $F(1/74)=0.001$; $P=0.97$). Groups differed significantly in their endocrine stress response over time (group × time interaction effect: $F(2.85/210.50)=6.10$; $P=0.001$, effect size $f^2=0.21$; Fig. 1), with subjects in the CBSM group showing an attenuated salivary cortisol response in comparison to controls.

In order to examine possible gender effects, gender was treated as an additional grouping variable. Results indicated that gender had a significant influence on cortisol responses (gender × time interaction effect: $F(2.92/210.31)=4.74$; $P=0.004$, effect size $f^2=0.21$). Furthermore, gender significantly interacted with group effects on cortisol responses over time (group × gender × time interaction effect: $F(3.85/277.20)=2.44$; $P=0.04$, effect size $f^2=0.20$). Therefore, group differences of cortisol responses over time in the TSST were analyzed separately for men (CBSM: $N=8$, controls: $N=10$) and women (CBSM: $N=31$, controls: $N=27$). Although both in men ($F(3.09/49.38)=4.37$, $P=0.008$, effect size $f^2=1.04$, see Fig. 2) and women ($F(2.69/150.40)=2.77$, $P=0.05$, effect size $f^2=0.15$, see Fig. 3) subjects of the CBSM group exhibited a significantly reduced cortisol response over time, the observed CBSM effect was of smaller magnitude in women.

Furthermore, the use of oral contraception was treated as an additional grouping variable in female subjects (CBSM: OC users: $N=15$, non-OC users: $N=14$, controls: OC users: $N=14$, non-OC users: $N=15$). Use of oral contraception had a significant effect on cortisol responses, with women using OC showing attenuated cortisol responses (OC use × time interaction effect: $F(2.51/135.54)=3.72$; $P=0.03$, effect size $f^2=0.18$), but not on the interaction between group and cortisol responses over time (OC use × group × time interaction effect: $F(2.51/135.54)=0.57$; $P=0.61$). Also, results of ANCOVA for repeated measures (with use of OC as covariate) indicated that use of OC did have an influence on cortisol responses in women (OC use × time interaction effect: $F(2.51/138.21)=3.32$; $P=0.03$). However, the inclusion of this covariate did not substantially influence the significance and magnitude of CBSM effect reported above (group × time interaction effect with OC use as covariate: $F(2.51/138.21)=2.69$; $P=0.06$, effect size $f^2=0.15$).

Subjects in the CBSM group had lower areas under the response curve with respect to increase (group effects: AUCi: all subjects: $F(1/75)=3.4$, $P=0.004$; Fig. 1, right-hand graph; men: $F(1/17)=1.3$, $P=0.09$, Fig. 2, right-hand graph; women: $F(1/57)=1.6$, $P=0.03$, Fig. 3, right-hand graph).

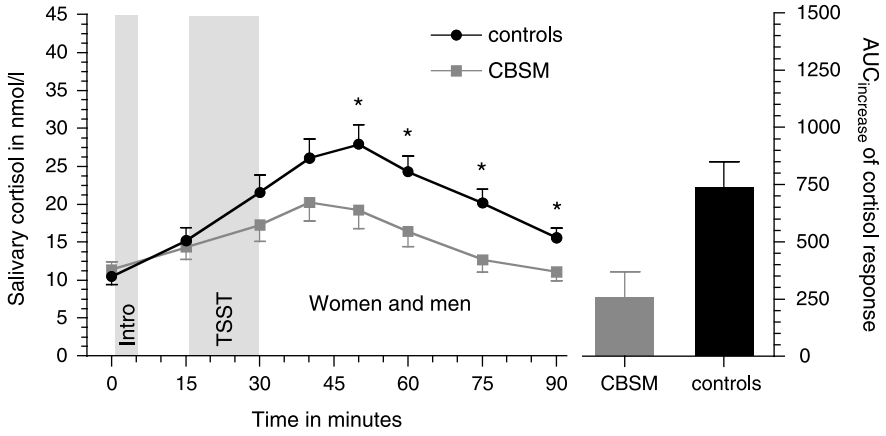

Figure 1 Cortisol responses to stress in all subjects (left-hand graph: repeated cortisol samples, right-hand graph: area under the response curve with regard to increase). *Indicate significance differences in pairwise comparison on the respective time point.

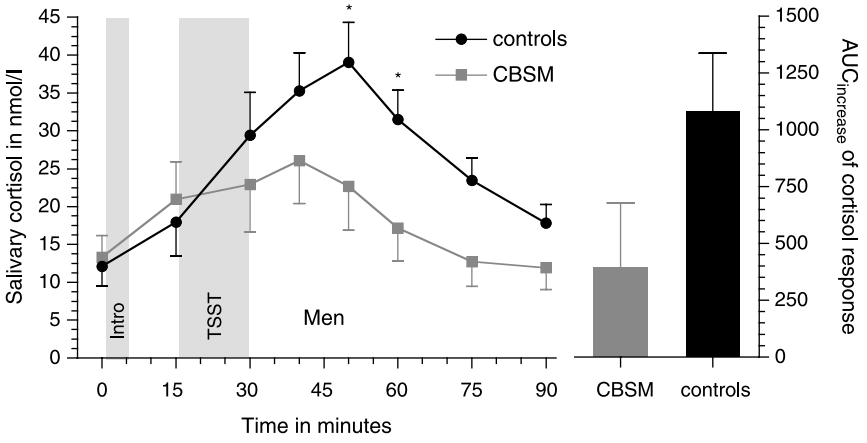

Figure 2 Cortisol responses to stress in men (left-hand graph: repeated cortisol samples, right-hand graph: area under the response curve with regard to increase). *Indicate significance differences in pairwise comparison on the respective time point.

Results of ANCOVA (with 'use of OC' as covariate) indicated that the use of oral contraception had no significant effect on AUCi in women (OC use effect: $F(1/57)=1.8$; $P=0.18$), and did not influence the observed differences between the CBSM and control group (group effect: $F(1/57)=0.7$; $P=0.41$).

Results of the ANOVA comparison indicated that groups differed significantly in their stress appraisal of the TSST, with lower scores in the CBSM group, indicative of lower stress appraisal (group effect: PASA 'Stress Index': CBSM: −1.24 (0.23) controls: −0.54 (0.27); $F(2/75)=4.7$; $P=0.01$, effect size $d=0.49$). The PASA 'Stress Index' between groups did not differ for men and women (group effect: $F(4/70)=0.77$; $P=0.56$). Analysis of covariance showed that cognitive appraisal had a significant effect on cortisol responses (PASA stress index×time interaction effect: $F(2.89/211.05)=3.81$, $P=0.01$, effect size $f^2=0.27$). Further analysis of covariance indicated that this effect was largely mediated through primary, but not secondary appraisal (PASA Primary Appraisal×time interaction effect: $F(2.80/208.42)=3.63$; $P=0.02$, $f^2=0.23$; PASA Secondary Appraisal×time interaction effect: $F(2.80/208.42)=0.67$; $P=0.69$). In addition, the inclusion of the PASA Stress Index as a covariate moderately reduced the observed effect size and level of significance, respectively (without covariate: see above; with covariate: $F(2.89/211.05)=4.93$, $P=0.04$, effect size $f^2=0.17$).

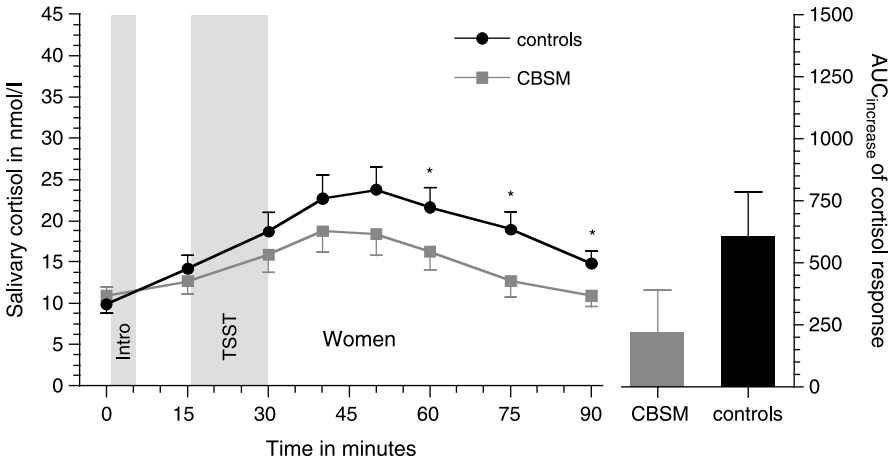

Figure 3 Cortisol responses to stress in women (left-hand graph: repeated cortisol samples, right-hand graph: area under the response curve with regard to increase). *Indicate significance differences in pairwise comparison on the respective time point.

4. Discussion

This study set out to examine the stability and the generalizability of CBSM effects on cortisol stress responses in healthy subjects.

With regard to the stability of endocrine CBSM effects over time, the results show that the previously observed attenuation of cortisol stress responses 2 weeks after CBSM training (Gaab et al., 2003) can also be observed after 4 months. The attenuation of the cortisol response to stress is seen in both men and women, although it should be noted that these effects are of a smaller magnitude in women. Comparable to previous findings, subjects in the CBSM group showed a reduced cognitive stress appraisal in the TSST. Furthermore, the observed cortisol response differences between groups were moderately influenced by differences in cognitive appraisal. With respect to the mediating effect of cognitive appraisal on the subsequent cortisol response, the proportion of variance of the cortisol response explained by the PASA score in this study was 27%. Although there are methodological differences between the studies, this figure replicates earlier findings of approximately 20–30% explained variance of cortisol stress responses through cognitive appraisal (19%, Gaab et al., 2003, 35%, Gaab et al., 2005). Confirming earlier observations (Gaab et al., 2003, 2005), primary appraisal had a stronger impact on cortisol stress responses than secondary appraisal. We have previously discussed possible psychobiological mechanisms of this observation (Gaab et al., 2005). However, it needs to be noted that this predominance of threat appraisal with respect to the activation of the HPA axis has important implications on differential indication. Thus, in order to reduce HPA axis stress responses, cognitive methods to assess, challenge and alter primary appraisal are clearly indicated.

It should be emphasized that the magnitude of cortisol response differences between groups was smaller than previously observed in a study with a 2-week interval between CBSM and TSST. This could represent a decline in the ability to retrieve and implement cognitive and behavioral strategies taught and practiced in the CBSM. However, several aspects speak against this assumption.

On the one hand, cortisol response differences between the CBSM and the control group were of a smaller effect size in women compared to men. This can be explained by the well-documented gender differences in HPA axis reactivity to stress, with attenuated HPA axis responses in women in general (Kirschbaum et al., 1992), thus reducing the likelihood of large effect sizes due to small responses per se. The most likely moderating candidate to account for this gender effect is the use of oral contraceptives, which have been shown to profoundly attenuate the cortisol stress response in women (Kirschbaum et al., 1999). On the other hand, the absolute cortisol response differences of men in this study were comparable to those seen in our previous study. Thus in the same gender, similar effects were seen two weeks as well as four months after the CBSM intervention.

It should be pointed out that we only measured saliva cortisol as an indicator for endocrine stress reactivity. Although saliva cortisol responses to stress have been shown to be closely associated to plasma cortisol and ACTH levels (Kirschbaum and Hellhammer, 1994), we cannot generalize our results on the HPA axis per se. The HPA axis is regulated by a multitude of factors on its different morphological levels, meaning that it would be beneficial to assess other HPA axis hormones, such as ACTH, arginine vasopressin and plasma cortisol in future studies.

Reductions of unstimulated cortisol levels after CBSM have been reported (e.g. breast cancer: Cruess et al., 2000). To the best of our knowledge, this is the first report of persisting endocrine effects of CBSM. It can be assumed that the protracted and beneficial effects of CBSM on clinical parameters and outcome (e.g. HIV: Antoni et al., 2002) are related to possibly persisting psychobiological consequences of these interventions. However, the possibility of differences in the CBSM and its effects between healthy subjects and patient populations remain to be elucidated in further studies. The finding of a profound and persisting attenuation of cortisol responses to stress through standardized and brief cognitive-behavioral intervention may have important implications, because similar interventions could be used to prevent short as well as long-term detrimental effects of stress-induced HPA axis responses.

However, we must caution against a oversimplified interpretation of our results in terms of 'less is better', since both hypo- as well as hypercortisolemic states have been linked to somatic and psychiatric conditions (McEwen, 1998; Ehlert et al., 2001; Fries et al., 2005). Also, there are no normative values for cortisol responses in the TSST. In our opinion, the examination of cortisol responses in the TSST in healthy subjects constitute a way to examine psychoneuroendocrine processes involved in development of HPA axis dysregulations, and therefore should not be mistaken as an indicator of dysregulations itself. Clearly, further

studies, preferably in high-risk populations, are needed.

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