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# Mood Changes in Response to Psychosocial Stress in Healthy Young Women: Effects of Pretreatment With Cortisol

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Effects of cortisol on human mood during stress situations are still incompletely understood, although this topic has important clinical implications. In this experiment, the mood of 44 healthy young women (all oral contraceptive users) was examined. A double-blind, randomized, placebo-controlled time series paradigm was used. Subjects were treated with either 30-mg cortisol or placebo orally. Forty-five minutes later, subjects attended a psychosocial stress procedure (Trier Social Stress Test; TSST; C. Kirschbaum, K. M. Pirke, & D. H. Hellhammer, 1993). The course of the subjects' mood as well as salivary cortisol and alpha-amylase levels were measured before and after the TSST. With regard to mood, it was found that the groups did not differ in mood before the TSST. After stress exposure, the subjective ratings of current mood state of cortisol-treated women were significantly less negative than that of placebo-treated subjects. These findings show that raising cortisol levels prior to acute stress has a protective effect on mood during stress situations. Results are discussed with regard to the context of specific adaptive effects of cortisol and the role of cortisol in posttraumatic stress disorder.

*Keywords:* cortisol, hypothalamic–pituitary–adrenal (HPA) axis, mood, stress, posttraumatic stress disorder (PTSD)

Cortisol in humans and corticosterone in rodents are the primary and most important glucocorticoids (GCs). Cortisol is synthesized in specific cells of the adrenal glands, released in the peripheral blood flow, and controlled in its production centrally by the complex feedback system of the hypothalamic–pituitary–adrenal (HPA) axis (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; McEwen, 2000; Sapolsky, Romero, & Munck, 2000). Different physiological and psychological stress situations lead to an enhanced activation of the HPA axis and result in an increased cortisol secretion. Besides their hormonal actions at the periphery of the body, GCs also influence multiple brain functions. A substantial amount of studies have investigated the effects of cortisol on cognitive functions like memory (Het, Ramlow, & Wolf, 2005; Lupien & McEwen, 1997), attention (Ellenbogen, Schwartzman, Stewart, & Walker, 2002; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999), or perception (Carpenter & Gruen, 1982; Erickson, Drevets, & Schulkin, 2003; Fehm-Wolfsdorf et al., 1993). Effects of the hormone on affective processes like mood have been investigated less frequently. These studies, however, may have important clinical implications for several psychiatric or neuroendocrine disorders (major depression, posttraumatic stress disorder [PTSD], Addison's disease, morbus Cushing).

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First, evidence that cortisol may influence mood was reported by Addison (1855), who observed depressive symptomatology in patients with adrenal insufficiency that cleared in response to cortisol replacement. Later, Stoll (1952) also linked euphoria to adrenal insufficiency. These historic reports show already that there appears to be no linear relationship between cortisol and mood. In line with these observations, patients with morbus Cushing, who have elevated cortisol levels in response to a tumor, show symptoms of depression or euphoria (Sonino & Fava, 2001). Similarly, patients undergoing chronic GC treatment report feelings of depression or euphoria (Brown & Suppes, 1998; Buchman, 2001; Ling, Perry, & Tsuang, 1981). It seems that hyper- as well as hypocortisolemia can be associated with pathological mood alternations. Of course, it has to be noted that these findings are from clinical studies and cannot be interpreted causally; therefore, placebo-controlled studies in healthy subjects are warranted. Previous studies on this topic can be divided into two groups. There are studies in which cortisol effects on mood under resting circumstances have been investigated as well as studies in which the relationship between cortisol and mood under circumstances of stress has been reviewed.

In studies conducted in resting experimental situations, it has been found that cortisol treatment sometimes leads to an enhancement of feelings of wakefulness and activity (e.g., Born, Hitzler, Pietrowsky, Pauschinger, & Fehm, 1988; Pietrowsky, Krug, Fehm, & Born, 1992; Wachtel & de Wit, 2001). However, several studies in which the effect of cortisol on memory performances was primarily investigated failed to reveal acute effects on mood (e.g., Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Buchanan & Lovallo, 2001; Buss, Wolf, Witt, & Hellhammer, 2004; Kuhlmann, Kirschbaum, & Wolf, 2005; Kuhlmann & Wolf, 2006; Monk & Nelson, 2002; Rimmele, Domes, Mathiak, & Hautzinger, 2003; Tops et al., 2003). It might be that the arousal

induced by the cognitive tasks or the anticipation has overruled potentially subtle acute cortisol effects on mood or arousal. In contrast, in several studies, more chronic (several days) treatment with GCs has led to dysphoric mood or negative emotions (e.g., Bender, Lerner, & Kollasch, 1988; Gift, Wood, & Cahill, 1989; McCabe & Corry, 1978; Plihal, Krug, Pietrowsky, Fehm, & Born, 1996; Schmidt et al., 1999; Sharfstein, Sack, & Fauci, 1982; Wolkowitz et al., 1990).

There are, however, studies in which cortisol's relationships to mood during stress has been investigated. These studies are based on the observation that stress situations lead to alterations in mood, usually in a negative direction. For example, Buchanan, al'Absi, and Lovallo (1999) observed an increase in a stress situation with negative affective quality (public speech task) and a decrease in a humorous situation (watching a laughter inducing film) with regard to salivary cortisol concentration. It has been oberved in other studies (e.g., al'Absi et al., 1997; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004; Kuhlmann, Piel, & Wolf, 2005) that stress leads to increased cortisol levels and a decrease in mood.

There is one study of healthy subjects in which cortisol concentrations are manipulated in order to investigate the effect of cortisol on mood during a potentially stressful situation. Reuter (2002) administered cortisol or placebo before exposing the subjects to a stress-inducing or a neutral movie. As expected, subjects under placebo scored higher in negative mood after viewing the negative movie. Cortisol led to reduced scores in anger and higher scores in joy and activity compared with placebo treatment. In the neutral-movie condition, cortisol selectively enhanced activity. Cortisol levels did not change in response to the stressful movie in subjects treated with placebo, indicating that this video-based stressor was not strong enough to increase HPA activity, a finding in agreement with a recent meta-analyis (Dickerson & Kemeny, 2004). Nevertheless, the data suggest that although cortisol acutely may not be able to induce a specific mood on its own, the hormone, however, could have adaptive functions that help one to cope emotionally with situations of under- or overstimulation (Reuter, 2002).

In line with this observation is a recent study reporting that patients with social phobia report reduced anxiety in a psychosocial stress paradigm (the Trier Social Stress Test; TSST) when treated with 25 mg cortisone before stress exposure (Soravia et al., 2006). The authors of the latter study suggest that the ability of cortisol to impair emotional memory retrieval (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005; Roozendaal, 2002) may be accountable for the positive effects. Phobic patients may retrieve less negative phobia-related memories after cortisol treatment.

The above-mentioned concepts could also be of relevance for PTSD. PTSD patients often have lower basal cortisol levels, probably reflecting an enhanced negative feedback (Yehuda, 2001). These neuroendocrine alternations may already be present prior to trauma exposure, possibly reflecting a vulnerable predisposition to stress (Yehuda et al., 2000, 2005). Placebo-controlled pilot studies in intensive care unit patients suggest that cortisol treatment may prevent the occurrence of PTSD in response to a life-threatening emergency procedure (Schelling, Roozendaal, & de Quervain, 2004). Moreover, low-dose cortisol treatment has beneficial effects on PTSD symptoms, which could reflect the impairing action on trauma-related memory retrieval as well as potentially adaptive functions on the affective tone of the patients (Aerni et al., 2004).

On the basis of these previous findings, we hypothesize that cortisol has protective effects on mood during a situation with strong emotional load (e.g., psychosocial stress). If cortisol plays an adaptive role in affect regulation during or after stress, then subjects who show high cortisol concentration before or during a stress situation, like the subjects of Reuter (2002) or Soravia et al. (2006), should cope better with the emotional load of such situations than subjects with a regular or even blunted cortisol secretion.

We tested this hypothesis in a double-blind, randomized, and placebo-controlled experiment. For this purpose, we administered cortisol or placebo, respectively, to young healthy women and investigated the course of the subject's mood states before and after a psychosocial stress paradigm. On the basis of the findings by Kirschbaum et al. (1999; Kirschbaum, Pirke, & Hellhammer, 1995; Kirschbaum, Wust, & Hellhammer, 1992), we included only women who used oral contraceptives in order to assure a blunted-free cortisol stress response. For the cortisol pretreatment, we chose a dosage of 30-mg cortisol, which is comparable with the doses used in previous experiments on this topic by Reuter (2002) and Soravia et al. (2006).

## Method

### *Subjects and Screening*

Forty-four healthy medication-free, female, nonsmoking volunteers with a mean age of 22.7 years ($SD \pm 2.5$) and a mean body mass index (BMI) of 21.1 ($SD \pm 2.2$) were recruited for this study among students of the University of Düsseldorf, Düsseldorf, Germany. All subjects used hormonal oral contraceptives (monophasic preparation, with an ethinylestradiol concentration between 0.02 mg and 0.035 mg, and a progesterone derivative), which leads to a blunted-free cortisol response in the used stress paradigm (Kirschbaum et al., 1999). Subjects were tested during the 15th and the 21st day of the intake of their oral contraceptives. The volunteers underwent a brief medical and psychological examination on a day prior to testing in order to check the following exclusion criteria: acute or chronic physiological or psychological diseases, age younger than 18 or older than 40 years, BMI (weight in kg/height in $m^2$) outside the normal range between 18 and 26, and previous experience with the stress protocol. To exclude subjects with depression, the German version of the Center for Epidemiological Studies Depression Scale (ADS-L; Hautzinger & Bailer, 1993), originally developed by Radloff (1977), was administered. Subjects above the cutoff sum score of 24 were excluded. Subjects were instructed to refrain from physical exercise and eating and drinking anything but water for 1 hr prior to testing. The subjects received detailed verbal and written information about the study and provided written consent. The study protocol was approved by the National Ethics Committee of the German Psychological Association.

### *Psychometric State Measures*

To assure the absence of pretreatment differences in trait measures between the experimental groups, all subjects had to com-

plete a German version of Costa and McCrae's (1992) questionnaire on the Big Five personality factors prior to the day of investigation: Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness (Revised NEO Personality Inventory; Ostendorf & Angleitner, 2004). A further questionnaire on the preferred stress coping strategies (Stressverarbeitungsfragebogen-120 [Stress Coping Inventory]; Janke, Erdmann, Kallus, & Boucsein, 1997) was used. This questionnaire measures whether someone makes use of stress-enhancing (negative strategies) or stress-reducing strategies (positive strategies). Finally, chronic stress was assessed with a German questionnaire (Trierer Inventar zur Erfassung von chronischem Stress [The Trier Inventory for the Assessment of Chronic Stress]; Schulz & Schlotz, 1998) that measured the dimensions workload, labor stress, social stress, absence of positive feedback, worries, and intrusive memories.

### *Experimental Design and Procedure*

This study is based on a double-blind, placebo control group design, with repeated measures of salivary cortisol, salivary alpha-amylase (sAA), and mood. The time course of the experiment is shown in Figure 1.

At first, after arrival at the laboratory, the subjects were asked about their current well-being, and their heart rate (HR), blood pressure (RR), and blood sugar were monitored in order to control whether the subjects refrained from physical exercise and eating prior to testing. Fifteen minutes later, subjects received orally placebo or 30-mg (3 times 10-mg) cortisol (hydrocortisone, Hoechst, Germany). Salivary samples were collected eight times (see Figure 1) with Salivette sampling devices (Sarstedt, Nümbrecht, Germany) because of measure-free salivary cortisol levels as a measure of HPA activity (Kirschbaum & Hellhammer, 1989, 1994) and to measure sAA as an indirect measure of the activity of the sympathetic nervous system (SNS; van Stegeren, Rohleder, Everaerd, & Wolf, 2005).

To examine the effects of cortisol treatment on subjective emotional experience in a stressful setting, current emotional state was measured five times (see Figure 1) using two questionnaires (see below).

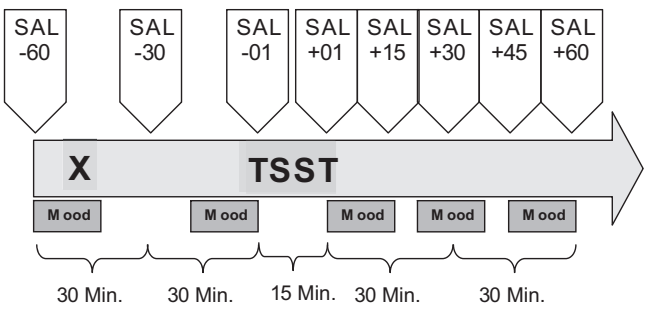


*Figure 1.* Outline of the experiment. One session took about 2 hr and 15 min. During this time, a total of eight saliva (SAL) samples were obtained, three before and five after the stressor (the Trier Social Stress Test; TSST). "Mood" stands for subjective mood rating with two questionnaires (the Profile of Mood States and Mehrdimensionaler Befindlichkeitsfragebogen [Multidimensional Mood questionnaire]; MDBF). The "X" indicates the point when cortisol (30 mg) or placebo was administered (15 min after arrival).

One hour after arrival at the laboratory, the subjects were exposed to a 12-min psychosocial stressor. The TSST was performed similarly to the description provided by Kirschbaum et al. (1993). The meta-analytical review by Dickerson and Kemeny (2004) showed that stress procedures like the TSST are quite effective in eliciting a significant HPA response. Beside this, in several studies, the TSST has been found to be effective in eliciting negative mood states (e.g., Kudielka et al., 2004; Kuhlmann, Piel, & Wolf, 2005). Forty minutes after the TSST, the subjects were debriefed by the committee. After 2.5 hr, the subjects were paid for their participation and asked to guess whether they had received cortisol or placebo. All experimental sessions took part in the late afternoon (4–7 p.m.), close to the circadian cortisol trough.

*Measurement of mood.* Current emotional state was measured five times. The questionnaires were given 15 min and 45 min after arrival at the lab and 1, 45, and 60 min after the stress procedure. The subjective mood ratings were obtained from the 24 adjectives in a German mood questionnaire (Mehrdimensionaler Befindlichkeitsfragebogen [Multidimensional Mood questionnaire; MDBF]; Steyer, Schwenkmezger, Notz, & Eid, 1997). The MDBF is a short, multidimensional, self-evaluative questionnaire that describes the current mood state of an individual on the three dimensions "good versus bad mood," "wakefulness versus sleepiness," and "calmness versus restlessness."

In addition, the 19 emotional adjectives from the German version of the Profile of Mood States (POMS; Dalbert, 1992), originally developed by McNair, Lorr, and Doppelman (1971), were used. The POMS measures current subjective mood states on the four mood dimensions "sadness," "hopelessness," "tiredness," and "anger." The scores of the first three dimensions can be summarized to a general scale of "current positive emotional state," which was used as an outcome measure in the present study. At all time points, the two questionnaires were given to each subject in randomized order.

*Saliva sampling and biochemical analysis.* Saliva samples were obtained 15 min before and 15 min after treatment and 1 min before and 1, 15, 30, 45, and 60 min after the TSST (see Figure 1).

Saliva was used to measure free cortisol as well as sAA levels and were collected using Salivette sampling devices. Samples were stored at −20 °C until biochemical analysis. Free cortisol levels were measured using a commercially available Luminescent-immunoassay (Immuno-Biological Laboratories, Hamburg, Germany). The sAA was measured by using a quantitative enzyme kinetic method, as described in detail elsewhere (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004). Inter- and intraassay variations were below 15%.

*Statistical analysis.* Initial group differences with regard to personality factors, amount of chronic stress, preferred coping strategies, HR, RR, blood sugar, age and BMI were analyzed using Wilcoxon's Mann-Whitney $U$ test and Student's $t$ test, respectively. Analyses of variance (ANOVA) for repeated measures were performed on the results of cortisol, sAA, and the subjective mood ratings to reveal possible time and/or treatment effects. If the assumption of sphericity was violated, then degrees of freedom were adjusted by using the Greenhouse–Geisser procedure. Specific time points of interest were analyzed with Student's $t$ test, and Hedges' unbiased effect size $d$ (Hedges & Olkin, 1985) was calculated for mood. The subjects' guess about their treatment was analyzed using Fisher's exact test for contingency tables. All

statistical calculations were performed using SPSS 11.0 for Mac OS X statistical package. Level of significance was overall defined as $p < .05$.

## Results

### *Description of the Sample*

The two groups did not differ with respect to age ($Mean_{Cortisol} = 22.23$ [± .50 *SEM*]; $Mean_{Placebo} = 23.64$ [± .56 *SEM*], $p = .07$) and BMI ($Mean_{Cortisol} = 21.16$ [± .50 *SEM*]; $Mean_{Placebo} = 21.07$ [± .45 *SEM*], $p = .90$). They also did not differ in any of the trait measures assessed with the psychological questionnaires prior to testing (data not shown). In addition, the subjects could not infer whether they had been treated with cortisol or with placebo. Only 4 subjects of each group thought to have been treated with cortisol, whereas 18 subjects of each group did not. Four subjects had to be excluded from the analysis of the sAA either because of very high values probably reflecting sample contaminations or because of an insufficient amount of sampled saliva. One of them also was excluded from the cortisol analysis.

### *Cortisol and sAA*

The TSST caused an activation of both the HPA and the SNS system, as can be seen by the data of cortisol and sAA shown in Table 1.

With regard to salivary cortisol, the cortisol and placebo group differed significantly at all times of measurement after the pharmacological treatment in their concentrations of salivary cortisol but did not differ at baseline. Thus, an ANOVA for repeated measures revealed a significant effect of time, $F(2.7, 111.1) = 19.1$, $p < .01$; group, $F(1, 41) = 73.4$, $p < .01$; and a Time × Group interaction, $F(2.7, 111.1) = 19.2$, $p < .01$. As shown in Table 1, the placebo-treated group showed a small but significant increase in salivary cortisol concentrations in response to the TSST. Comparing the salivary cortisol concentration 1 min before the TSST with its concentration 15 min after this stress procedure within the control group, the paired $t$ test revealed a significant result, $t(21) = -3.3$, $p < .01$. The cortisol-treated subjects showed a significant increase in salivary cortisol concentration at all time points after treatment compared with their own baseline and the placebo group ($ps < .01$).

With regard to the sAA, the groups were similar at baseline, as shown in Table 1. Both groups showed an increase after the TSST. An ANOVA for repeated measures revealed a significant effect of time, $F(2.5, 93.6) = 16.3$, $p < .01$, and a nonsignificant effect of a Time × Group interaction, $F(2.5, 93.6) = 1.5$, $p = .23$. On a descriptive level, cortisol-treated subjects appeared to show a less pronounced rise in sAA, but this failed to reach significance.

### *Subjective Mood Ratings*

Cortisol pretreatment had an effect on mood reported immediately after stress. For the dimension "bad versus good mood," the cortisol-treated group showed higher values than the placebo-treated group. This indicates that they were less affected by the stress exposure. The groups were similar at baseline but began to differ after stress exposure. On the "bad versus good mood" dimension, shown in Figure 2, the groups differ significantly 1 min after the TSST, $t(42) = -2.3$, $p < .05$. Hedges' unbiased effect size was $d = 0.68$. An ANOVA for repeated measures, however, revealed a significant effect of time, $F(2.9, 119.8) = 21.2$, $p < .01$, but only a trend for the Time × Group interaction, $F(2.9, 119.8) = 2.1$, $p = .1$.

The differences between both groups on the "wakefulness versus sleepiness" dimension and on the "calmness versus restlessness" dimension at the time point 1 min after the TSST were not significant ($p > .05$). Again, ANOVAs for repeated measures revealed only a significant main effect of time (data not shown).

Table 1
*Salivary Cortisol and Alpha-Amylase Levels of Cortisol- and Placebo-Treated Subjects During the Course of the Experiments*

| | Salivary cortisol | | | | Salivary alpha amylase | | | |
|---|---|---|---|---|---|---|---|---|
| | Cortisol group | | Placebo group | | Cortisol group | | Placebo group | |
| Variable | *M* | ±*SEM* | *M* | ±*SEM* | *M* | ±*SEM* | *M* | ±*SEM* |
| Time before TSST | | | | | | | | |
| −60 | 5.71 | 0.75 | 5.70 | 0.45 | 41.85 | 8.34 | 37.20 | 6.73 |
| −45[a] | | | | | | | | |
| −30 | 141.14[b] | 32.95 | 5.54 | 0.44 | 45.79 | 7.56 | 39.64 | 6.08 |
| −01 | 223.04[b] | 36.95 | 4.98 | 0.37 | 41.22 | 6.17 | 38.15 | 6.93 |
| Time after TSST | | | | | | | | |
| +01 | 189.22[b] | 26.85 | 5.00 | 0.36 | 78.65 | 15.49 | 100.43 | 17.82 |
| +15 | 173.71[b] | 25.40 | 6.55 | 0.53 | 38.23 | 5.63 | 47.71 | 7.91 |
| +30 | 206.89[b] | 22.04 | 6.09 | 0.59 | 38.36 | 5.76 | 50.08 | 8.24 |
| +45 | 224.28[b] | 19.44 | 5.64 | 0.47 | 47.44 | 8.39 | 43.35 | 6.98 |
| +60 | 217.28[b] | 19.04 | 5.08 | 0.39 | 45.02 | 8.36 | 45.66 | 7.37 |

*Note.* Salivary samples were collected before the Trier Social Stress Test (TSST) in 30-min and after the TSST in 15-min intervals. Both groups showed a significant increase in salivary alpha-amylase (sAA) levels in response to the TSST, but the two treatment groups did not differ significantly in their sAA levels over the course of the study.

[a] Represents time when pharmacological treatment (oral cortisol or oral placebo) took place. [b] Significant increase (compared with the baseline and placebo-treated group) in the cortisol group after treatment.

Results of the POMS scale "current positive emotional state" are shown in Figure 3. Similar to the "good versus bad mood" dimension of the MDBF, the cortisol-treated subjects showed, on average, higher values than the placebo-treated group after the TSST. The groups differed significantly immediately after the TSST, $t(42) = -1.7$, $p < .05$. Hedges' unbiased effect size was estimated with $d = 0.51$. An ANOVA for repeated measures showed no significant effect of time, $F(2.7, 108.4) = 1.7$, $p > .05$, or Time × Group interaction, $F(2.7, 108.4) = 1.4$, $p = .26$, but a trend for the effect of group, $F(1, 40) = 3.1$, $p = .08$. On a descriptive level, cortisol-treated subjects reported more positive emotional state at all three measurements after stress.

### *Associations Between Subjective Mood Ratings and sAA Levels*

In order to test whether changes in sAA levels (delta increase in response to the stressor) were associated with changes in mood (delta decreases in MDBF and POMS scores), several correlations were performed. Neither for the entire sample nor for the two treatment groups were significant correlations between sAA changes and mood changes observed (data not shown).

## Discussion

The goal of the present study was to investigate the influence of pharmacologically increased cortisol level on the course of the current mood state of female oral contraceptives users participating in a psychosocial stress paradigm. On the basis of previous work (Reuter, 2002; Soravia et al., 2006), we expected that cortisol pretreatment might have a stress-buffering effect on mood.

The neuroendocrine results show that, as expected, female subjects who were treated with 30-mg cortisol showed a significant strong increase in salivary cortisol concentration 30 min after cortisol treatment. Cortisol levels in this group remained significantly elevated throughout the course of the study and were similar to previous studies from our laboratory (Kuhlmann & Wolf, 2006). These levels were in the upper physiological range, as induced by severe stress (Deinzer, Kirschbaum, Gresele, & Hellhammer, 1997; Fenz & Epstein, 1967; Leino, Leppaluoto, Ruokonen, & Kuronen, 1999a, 1999b; Roth, Breivik, Jorgensen, & Hofmann, 1996; Schedlowski & Tewes, 1992).

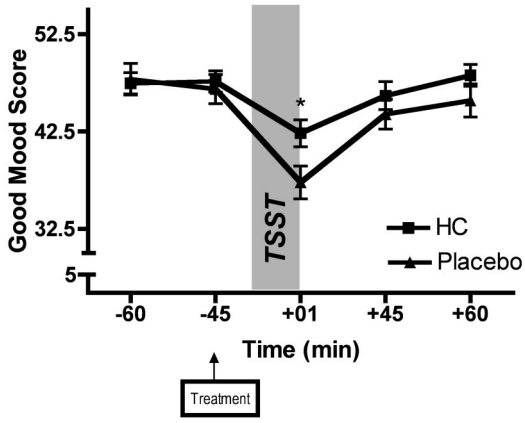


*Figure 2.* Results of the Mehrdimensionaler Befindlichkeitsfragebogen [Multidimensional Mood questionnaire] (MDBF) for women treated with cortisol or placebo before being exposed to a laboratory stressor (the Trier Social Stress Test; TSST). The values of the *x*-axis (Time) indicate the minutes prior to stress exposure (− 60 and −45) and the minutes poststress exposure (+01, +45, +60). The stressor had a length of 15 min. The curves show means and their standard errors of the "bad versus good mood" dimension of the MDBF. Higher scores indicate more positive mood. HC = hydrocortisone. $^{*}p < .05$ in the planned single comparison between the placebo- and cortisol-treated group.

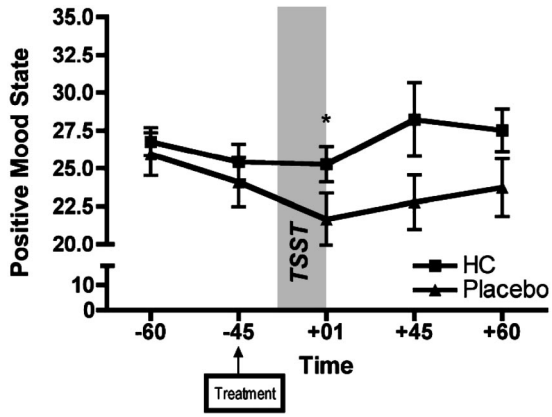


*Figure 3.* Results of the Profile of Mood States (POMS) for women treated with cortisol or placebo before being exposed to a laboratory stressor (the Trier Social Stress Test; TSST). The values of the *x*-axis (Time) indicate the minutes prior to stress exposure (− 60 and −45) and the minutes poststress exposure (+01, +45, +60). The stressor had a length of 15 min. The curves are the means and their standard errors and describe the POMS dimension "current positive mood state." The higher the score, the more positive is the current mood. HC = hydrocortisone. $^{*}p < .05$ in the planned single comparison between the placebo- and cortisol-treated group.

Subjects of the placebo group showed a mild but significant increase in salivary cortisol levels in response to the stressor, which is in line with previous studies investigating women using hormonal contraceptive. As found by Kirschbaum et al. (1999, 1995, 1992), oral contraceptive use leads to a blunted increase in free salivary cortisol levels in response to acute stress. In contrast, the ACTH response as well as the total cortisol response determined out of serum are similar to that of naturally cycling women (Kirschbaum et al., 1999). We decided to study these subjects in order to investigate the effects of cortisol on mood in the context of a blunted acute reactivity of HPA. Future studies are needed in order to test the occurrence of similar effects in naturally cycling women or men.

The results on the sAA show that a general increase in sAA in response to the TSST is in line with previous findings (Nater, La Marca et al., 2005; Nater, Rohleder et al., 2005). Cortisol-treated subjects had, on a descriptive level, a smaller stress-induced increase than placebo-treated subjects. This would indicate a reduced response of the SNS in response to stress, which would be in line with the subjective mood ratings. However, this difference is not significant, and therefore one may only cautiously think that enhanced cortisol levels reduce adrenergic reactivity. It is interesting to note that Soravia et al. (2006) also observed a trend toward a reduced (or delayed) HR increase in combination with a faster HR

recovery in their phobic patients treated with cortisone prior to social stress exposure.

The present study's results on the subjective mood ratings show that cortisol-treated subjects developed, on average, less negative mood states compared with placebo-treated subjects after acute stress exposure. After the stress situation, both groups showed a decrease in positive mood ("bad versus good mood" dimension of the MDBF), but the decrease was less pronounced in cortisol-treated subjects. Therefore, cortisol-treated subjects reported significantly more positive mood directly after stress. The same results were obtained on the "positive mood" dimension of the POMS. Furthermore, the results on both the POMS and MDBF show that the groups did not differ in subjective ratings after cortisol treatment. This suggests that there is no acute effect of cortisol treatment on mood in a resting situation, which is in line with previous observations (e.g., Pietrowsky et al., 1992). The groups differed only in current mood states immediately after the TSST and tended to do so for the rest of the course of the experiment. The conducted ANOVAs, which included all five measurement points during the course of the study, only revealed trends for a Cortisol $\times$ Time interaction (MDBF) or a cortisol main effect (POMS). This can be attributed to the fact that the effects were only observable immediately after stress exposure at a time when the placebo group reported a strong decrease in positive mood. Effect size calculations for this time point revealed that the effects were at least 0.5 in size (i.e., subjects treated with cortisol differed from subjects treated with placebo in their subjective mood ratings, on average, at least half a standard deviation). According to Cohen (1988), these effects can be considered as moderate effects. The two groups did not differ in dimensions of wakefulness and calmness, which may indicate that cortisol treatment does not influence these dimensions of mood in a psychosocial stress situation.

The reduction in stress-induced negative affect under the condition of high cortisol is in line with the experimental findings of Reuter (2002) in healthy male subjects and Soravia et al. (2006) in phobic patients. Reuter (2002) reported only on trends or significant effects if alpha level is defined as .1. Soravia et al. (2006) found a significant reduction in self-reported fear of patients with social phobia who attended the TSST and were treated before with cortisone (25 mg). Similar to these researchers, we found that increasing cortisol levels leads to a reduction in stress-induced negative affect. The present study as well as the previous studies just discussed used medium to large doses of cortisol (20–40 mg). It therefore remains to be investigated whether a smaller cortisol dose (e.g., 5 mg) also has stress protective properties on mood.

Some of the differences between the present study's findings and that of Reuter (2002) can probably be attributed to the stress procedure Reuter (2002) used in contrast to ours and the experiment of Soravia et al. (2006). As elaborated in detail by the meta-analytical findings of Dickerson and Kemeny (2004), laboratory stress procedures combining socioevaluative threat with uncontrollability are more effective in activating the HPA axis than stress-inducing films, as used by Reuter (2002). Nevertheless, these findings on cortisol effects on mood under stress conditions are in line with Reuter's (2002) assumption of a protective effect of cortisol on mood in the context of stress.

Our results as well as those of the two previous studies could suggest that an anticipatory cortisol increase prior to a stressful event may be adaptive because it could reduce or abolish the negative effects of the stressful situations on mood. This may help coping with the stress situation. In fact, several previous studies have observed strong anticipatory cortisol increases prior to announced stressful events (e.g., an oral exam). However, these changes have not been consistently linked to the impact of the stressor on mood (e.g., Armario, Marti, Molina, de Pablo, & Valdes, 1996; Lacey et al., 2000).

Whether the present study's findings also indicate that a stronger cortisol response during a stressful episode has stress protective effects on mood or anxiety remains to be established. Soravia et al. (2006) observed in her placebo-treated phobic patients that a higher cortisol stress response was associated with a smaller increase in self-reported anxiety. Having said this, most studies with healthy nonpsychiatric subjects reported either no association between the cortisol response and changes in mood or a stronger decrease in mood in those subjects showing a more pronounced HPA stress response (e.g., Kudielka, Schmidt-Reinwald, Hellhammer, Schurmeyer, & Kirschbaum, 2000; von Känel et al., 2005).

One might speculate that the present findings could be of relevance for stress-associated psychiatric conditions like PTSD. In an extreme stress situation, reduced basal cortisol levels and/or a blunted cortisol stress response may lead to stronger and maybe more persistent changes in affect. Thus, people who chronically show a blunted HPA (re)activity and experienced enormous stress situations like a trauma could be more vulnerable to developing PTSD. This hypothesis would be in line with observations of reduced basal cortisol levels in these patients (Yehuda, 2002). More support comes from observations that lower cortisol levels after trauma are predictive of the future development of PTSD (Delahanty, Raimonde, & Spoonster, 2000). In addition, PTSD can be prevented with cortisol treatment in an intensive care unit setting (Schelling et al., 2004). Finally, initial evidence has been presented that low-dose cortisol treatment might reduce some of the core PTSD symptoms (Aerni et al., 2004). In the context of PTSD, however, effects of cortisol on emotional memory retrieval have also to be considered (Aerni et al., 2004).

A remaining question is how these stress protective and adaptive effects of cortisol might be mediated. Several possible mechanisms should be discussed briefly. Cortisol binds to the glucocorticoid receptor (GR), which is distributed widely in the brain, including in the prefrontal cortex (PFC), and with higher affinity to the mineralocorticoid receptor (MR), which is mostly concentrated in limbic areas (De Kloet, Oitzl, & Joels, 1999; De Kloet, Ratka, Reul, Sutanto, & Van Eekelen, 1987; De Kloet et al., 1998). In addition, cortisol can influence several catecholaminergic (adrenergic, dopaminergic, serotonergic) neurotransmitter systems via rapid nongenomic mechanisms (Joels, 2000).

Davidson (2002; Davidson & Irwin, 1999) and Dolan (2002) showed that emotional processes involve a complex neural network involving the PFC, amygdala, insula, basal ganglia, and anterior cingulate. The PFC has been especially linked to the control of the amygdala (Davidson, 2002) and the HPA axis stress response (Diorio, Viau, & Meaney, 1993). It could be that cortisol treatment before the TSST has modulated these pathways, resulting in a significant difference in the emotionality of placebo- and cortisol-treated subjects after stress. Wang et al. (2005) provided neuroimaging evidence that the cerebral blood flow of the right ventral PFC and the left insula/putamen area increases during

stress. These activations correlated positively with subjective stress ratings, cortisol level, and HR. It may be that the effects of cortisol on the PFC reduce the emotional response to stress. Of course, this behavioral study does not allow researchers to conclude what brain region is crucial in mediating the stress protective effects of cortisol pretreatment observed in the present study. Thus, neuroimaging studies on this topic are warranted.

A further hypothesis to explain the results of the present study could focus on central extrahypothalamic corticotropin-releasing hormone (CRH) systems, which are crucially involved in anxiety (Landgraf, 2005) and depression (Mitchell, 1998; Nemeroff, 1996). It has long been recognized that CRH is not only involved in the initiation of the neuroendocrine stress response but also acts as a neurotransmitter in the CNS. Of special relevance for the present findings are the innervations of noradrenergic systems in the locus coeruleus (LC) and the central nucleus of the amygdala (Mitchell, 1998). These areas are crucially involved in anxiety and the emotional response to stress. Cortisol exerts negative feedback on hypothalamic neurons; thus, cortisol-treated subjects of the present study may have had reduced negative affect resulting from a reduced central CRH secretion in response to the stressor. However, in conditions of chronically elevated GC levels, the activity of the CRF system in the amygdala is increased rather than decreased (Schulkin, Morgan, & Rosen, 2005).

Another possible explanation for the effects of cortisol on mood after stress is based on the fact that cortisol administration reduces emotional memory retrieval when administered before retention testing (Buchanan, Tranel, & Adolphs, 2006; Het et al., 2005; Kuhlmann, Kirschbaum, & Wolf, 2005; Kuhlmann, Piel, & Wolf, 2005; Roozendaal, Okuda, de Quervain, & McGaugh, 2006). Memory retrieval may play a role in coping with experiences of stress, and so indirectly may influence mood as well. The more positive mood of subjects treated with cortisol may result from a slight impairment in retrieving the just-experienced negative stress episode and/or from a reduced retrieval of previous negative episodes related to the stressor. Cortisol-treated subjects may be prevented from reflecting on their mistakes and perceived failure in the TSST situation, and this might protect them from a decrease in positive affect state after stress. According to this hypothesis, Soravia et al. (2006) suggested that elevated cortisol levels may reduce stimulus-induced fear of phobic subjects by inhibiting retrieval of previous fearful episodes. The authors speculated that beneficial effects of cortisol for the prevention (Schelling et al., 2001, 2004) or treatment (Aerni et al., 2004) of PTSD might be mediated by a similar mechanism.

Of course, the present study has to be replicated, and additional research is needed. We only tested women who were using oral contraceptives, so research in naturally cycling women is warranted. In this context, there should also be an analysis of possible gender differences with regard to these findings because previous studies of emotional responding have found that women are more emotionally expressive than men and that there are differences in processing (Hamann & Canli, 2004; Kring & Gordon, 1998).

We tested all subjects in the late afternoon, a time when endogenous basal cortisol levels are relatively low. Because the effects of stress on mood may be dependent on the time of day (Kudielka et al., 2004), studies conducted in the morning would be informative. In addition, we only assessed the effects on mood. Future studies might consider using a broader psychometric approach by including measures of anxiety, aggression, depression, and the like. The descriptive observation that cortisol-treated women had lower sAA levels also calls for a more elaborate assessment of SNS reactivity during stress (e.g., HR, HR variability, plasma catecholamine levels) in future studies on this topic. It would also be interesting to investigate potential brain correlates of these effects using functional magnetic resonance imaging, positron emission tomography, electroencephalograpy (see, e.g., Schmidt et al., 1999; Wang et al., 2005) in a similar experiment. Such an investigation would allow a localization of the stress-buffering effects of cortisol in the human brain. On the basis of previous observations, effects on the PFC as well as the limbic system are conceivable.

In summary, we report the first experimental study on the effects of cortisol pretreatment on psychosocial stress-induced mood changes in healthy young women. The present study's results suggest that cortisol has a beneficial and adaptive effect in this context by preventing or reducing stress-associated mood impairments. The findings indicate that the stress-reducing effect of cortisol pretreatment is not restricted to phobic populations (Soravia et al., 2006). Furthermore, the present findings could be of relevance for a better understanding of the development of PTSD in trauma-exposed people with a reduced basal or a reduced stress responsive HPA system.

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