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Glucocorticoids do not reduce subjective fear in healthy subjects exposed to social stress

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ABSTRACT

Background: Previous experiments in patients with phobia have shown that the administration of glucocorticoids reduces fear in phobic situations. Extensive evidence indicates that elevated glucocorticoid levels inhibit memory retrieval processes. In patients with phobia, exposure to a phobic stimulus (socio-evaluative stress test) provokes retrieval of stimulus-associated fear memory that leads to a fear response. It is therefore possible that glucocorticoids reduce phobic fear by inhibiting retrieval of the previously acquired fear memory. Whether glucocorticoids reduce subjective fear also in healthy subjects exposed to a socially fearful situation is not known.
Method: In a double-blind, placebo-controlled study, 50 healthy subjects underwent the same socio-evaluative stress test as used in a previous study in patients with social phobia. One hour before the stress test, subjects received 25 mg cortisone or placebo orally. Psychological anxiety measures were repeatedly assessed.
Results: Although the stress situation robustly increased fear in this population of healthy subjects, cortisone treatment did not reduce subjective fear, physical discomfort or avoidance behavior when compared to placebo-treated subjects.
Conclusion: The present study did not find evidence indicating that glucocorticoids reduce subjective fear in healthy subjects exposed to a socially fearful situation.

1. Introduction

Stress leads to a cascade of physiological responses, including the release of glucocorticoids (GCs), which ensure an appropriate adaptation to the changed internal and external environment (de Kloet et al., 1999; McEwen, 1998). Many studies using GCs have shown that these hormones can induce enhancing as well as impairing effects on memory. While GCs enhance memory consolidation (Buchanan and Lovallo, 2001; Cahill et al., 2003), they are known to impair the retrieval of already stored information (de Quervain et al., 1998, 2000; Het et al., 2005). Furthermore, there is evidence suggesting that emotional information is especially sensitive to the retrieval-impairing effects of glucocorticoids (e.g. de Quervain et al., 2007; Domes et al., 2004; Kuhlmann et al., 2005). In line with these findings, cortisol treatment for one month has been found to reduce retrieval of traumatic memories in patients with posttraumatic stress disorder (Aerni et al., 2004). Further studies from our laboratory showed that the acute administration of glucocorticoids before confrontation with a phobic stimulus reduces fear symptoms in phobic patients (Soravia et al., 2006). Exposure to a phobic stimulus provokes retrieval of stimulus-associated fear memory, which leads to the fear response (Cuthbert et al., 2003). In addition, phobic individuals tend to construct highly negative images of a phobic situation, which substantially contributes to anticipatory anxiety and negative post-event processing. Such images are usually associated with explicit fearful memories of past phobic experiences and reinforce negative beliefs that are difficult to suppress and may strengthen the phobic response (Mineka and Öhman, 2002). It is therefore possible that glucocorticoids reduce phobic fear through an inhibition of fear memory retrieval. Consequently, in healthy subjects, in whom no phobic fear memory exists, glucocorticoids might not exert anxiolytic effects when exposed to a fearful situation.

In the present study, we investigated the effect of a single oral administration of 25 mg cortisone on the fear response in healthy subjects using the same experimental design as in our previous study with socially phobic patients (Soravia et al., 2006). The

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design comprises the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) as a standardized socio-evaluative stressor.

2. Methods

2.1. Subjects and screening

Fifty-four healthy medication-free volunteers (females 18, males 36) with a mean age of 28.9 years (SD ± 6.13) were recruited for the study through advertisements. Individuals were screened via telephone and if preliminarily eligible, underwent a brief medical and psychological examination before testing in order to check the following exclusion criteria: presence of acute or chronic physiological diseases or clinically significant psychiatric disorders, smoking more than 15 cigarettes per day, and previous participation in a stress test. All female subjects had regular menses, were free of hormonal contraceptives, and the experiment was conducted during the luteal phase (between day 17 and day 25) of their menstrual cycle. In addition, subjects were screened for general psychiatric disorders using the German version of the *Symptom Checklist by Degoratis* (SCL-90-R) (Franke, 1995). Subjects who remained eligible at the end of the diagnostic phase were randomly assigned to a double-blind, placebo-controlled design. Subjects were informed about all study procedures before written informed consent was obtained. The study was approved by the ethics committee of the University of Zurich, Switzerland.

2.2. Experimental design and procedure

In a double-blind, placebo-controlled design, participants were orally administered with either 25 mg cortisone (Novartis Pharma, Basel, Switzerland) or placebo. Subjects were instructed to refrain from physical exercise and alcohol intake during the 24 h before the experiment and to abstain from eating anything for 1 h prior to testing. The experiment took place in the Department of Psychology of the University of Zurich between 14:00 h and 17:00 h to control for diurnal changes in cortisol secretion, and lasted approximately 3 h. The study consisted of three consecutive phases shown in Fig. 1: (1) an initial 60-min resting period to allow absorption of medication cortisone, which is quickly metabolized into hydrocortisone (cortisol), (2) a socio-evaluative stress test (30 min), and (3) a final 60-min recovery and debriefing period. After the experiment, participants were asked to guess whether they received cortisone or placebo and received 50 Swiss francs for their participation.

The standardized stress exposure TSST (Kirschbaum et al., 1993) begins with a written instruction informing the subjects that they have 10 min to prepare for a job interview in which they are required to explain within 5 min why somebody should hire them. The speech task is followed by an unprepared 5-min mental arithmetic task during which subjects are asked to continuously subtract 17 from 2043. Upon every mistake, the subjects have to start over again from the beginning. Numerous studies indicate that the TSST enables a naturalistic exposure to a socio-evaluative stressful situation, with significant increases in hypothalamic–pituitary–adrenal (HPA) axis and negative mood states (Dickerson and Kemeny, 2004; Heinrichs et al., 2001, 2003; Kuhlmann et al., 2005). To examine the effects of the glucocorticoid administration on subjective anxiety experienced in a stressful setting, the current emotional state was measured repeatedly (see Fig. 1) using various questionnaires.

2.3. Measurement of anxiety

Fear-related symptoms were repeatedly assessed over the course of the experiment (see Fig. 1). Subjects rated their subjective current discomfort in the dimensions anxiety, physical reaction and avoidance behavior seven times during the procedure using a Visual Analog Scale ranging from 0 (no symptoms) to 10 (maximal symptoms). State anxiety was measured using the German version (25) of the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). This questionnaire measures acute subjective anxiety at the moment of assessment. Furthermore, mood was assessed using the mood questionnaire (MDBF) consisting of three scales termed elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness (Steyer et al., 1997).

2.4. Saliva sampling and biochemical analysis

The procedure of collecting saliva (Sarstedt Inc., Rommelsdorf, Germany) was demonstrated to the participants, and was followed by the first sample collection before substance administration. Six additional saliva samples were collected 60, 70, 100, 110, 125, and 145 min after substance administration (see Fig. 1) in order to measure free cortisol. Samples were stored at −20 °C until required for biochemical analysis. The free cortisol concentration in saliva was analyzed using a commercially available chemiluminescence immunoassay (CLIA; IBL-Hamburg, Germany). The inter- and intra-assay coefficients of variation were below 10%.

2.5. Statistical analysis

Group differences in demographic and clinical characteristics and baseline values (before substance administration) were analyzed with unpaired *t*-tests. Effects of cortisone treatment on salivary cortisol concentrations, fear symptoms and mood were analyzed with repeated measures ANOVAs with treatment as between-subject factor and the repeated measurements as within-subject factor. Furthermore, as effect size measure ETA^2 is reported. Univariate ANOVAs and Student's *t*-tests were conducted to analyze treatment effects at a certain time point. Fisher's exact test for contingency tables was used for the analysis of the subjects' guess regarding their treatment. All tests were two-tailed and a probability of less than 0.05 was considered significant. All variables were normally distributed (Kolmogorov–Smirnov's test: $p > 0.1$, for all variables). All statistical calculations were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Description of the sample

The two groups consisted of 24 subjects in the cortisone group (8 females, 16 males) and 26 subjects in the placebo group (8 females, 18 males). The subjects of the two treatment conditions (cortisone vs. placebo) did not differ significantly in age (age: $Mean_{Cortisone}$ = 27.92 (±1.15 SEM); $Mean_{Placebo}$ = 29.81 (±1.28 SEM), p = .28), with respect to demographic and clinical characteristics, or in any of the baseline measurements on the day of the experiment ($p \geq .08$). Four subjects had to be excluded due to ineffective elevation of cortisol levels following cortisone administration. Whereas in our previous study, we investigated only males (N = 21), the present study investigated both males (N = 34) and females (N = 16). Gender-specific analysis did not show any differences between female and male participants in the baseline measurements or in any subsequent analyses. The groups did not differ in smoking status (p = .1) and inclusion of smoking as a covariate did not change any of the baseline measurements or any of the subsequent analyses.

Subjects were not able to infer whether they had been treated with cortisone or placebo (p = .75; Fisher's exact test). Seven subjects of the cortisone group and six subjects of the placebo group believed that they had been treated with cortisone.

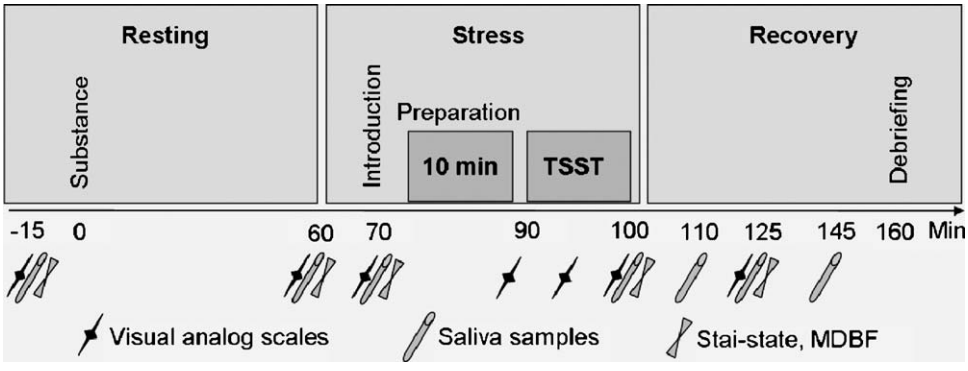

Fig. 1. Outline of the experiment. Subjects underwent the Trier Social Stress Test (TSST). Cortisone (25 mg) or placebo was administered orally 1 h before the stressor, and salivary cortisol levels and subjective fear were repeatedly measured. *T*: time (min) in relation to the time point of substance administration at *T*0.

Table 1
Salivary cortisol levels of the cortisone- and placebo-treated subjects during the course of the experiment.

Variable	Salivary cortisol (nmol/l)			
	Cortisone group ($N = 24$)		Placebo group ($N = 26$)	
	M	±SEM	M	±SEM
Time −15	12.55	1.10	13.05	1.65
60	44.90	4.72	9.38	1.08
70	50.11	4.89	8.05	0.82
100[a]	49.73	4.27	14.16	1.92
115[a]	47.09	4.06	20.55	2.54
125[a]	45.95	3.93	18.63	2.56
145[a]	46.27	4.41	13.07	1.63

Note: Salivary samples were collected 15 min before substance administration and then six times after (60, 70, 100, 115, 125, 145 min after). The placebo group showed a significant increase in salivary cortisol concentration in response to the TSST, whereas the cortisone group showed a significant increase in response to the cortisone administration.

[a] Saliva sample after the stress test (TSST).

3.2. Cortisol responses

The TSST caused a significant activation of the HPA system as shown in Table 1. With the exception of the first saliva sample at baseline, the cortisone and placebo groups differed significantly in their concentration of salivary cortisol at all times of the measurement after substance administration. ANOVA for repeated measures showed a significant main effect of time ($F = 25.0$; d.f. = 3.13, 150.2; $p < .001$), group ($F = 66.88$; d.f. = 1, 48; $p < .001$) and a time × group interaction ($F = 23.70$; d.f. = 3.13, 150.2; $p < .001$), with higher levels of saliva cortisol in the subjects treated with cortisone. The TSST provoked a significant increase of salivary cortisol concentration in the placebo group as calculated with a paired t-test (comparing the sample before TSST with 1 min after TSST: $t(25) = -3.41$, $p = .002$; and 15 min after TSST $t(25) = -5.34$, $p < .001$). The subjects with a pharmacologically elevated cortisol level showed a significant increase in the salivary cortisol concentration at all time points compared to their baseline ($p < .001$).

3.3. Fear responses

To analyze possible effects of the cortisone treatment on fear-related symptoms (anxiety, physical discomfort, avoidance), ANOVAs for repeated measures were carried out with treatment (cortisone vs. placebo) as between-subject factor and time (anxiety measurements at different time points) as within-subject factor. The analyses consistently showed a significant increase in the different fear dimensions during stress exposure (time effect: Visual Analog Scale *Anxiety*: $F = 29.94$; d.f. = 3.88, 185.98; $p < .001$, $\eta^2 = .384$; Visual Analog Scale *Physical Reactions*: $F = 16.69$; d.f. = 3.99, 191.79; $p < .001$, $\eta^2 = .258$; Visual Analog Scale *Avoidance*: $F = 17.27$; d.f. = 2.94, 140.91; $p < .001$, $\eta^2 = .265$; STAI-State: $F = 3.15$; d.f. = 3.18, 152.62; $p = .024$, $\eta^2 = .062$) (see Figs. 2–5). However, cortisone treatment had no effect in any of the measurements (treatment effect: Visual Analog Scale *Anxiety*: $F = .44$; d.f. = 1, 48; $p = .51$, $\eta^2 = .009$; Visual Analog Scale *Physical Reactions*: $F = .274$; d.f. = 1, 48; $p = .603$, $\eta^2 = .006$; Visual Analog Scale *Avoidance*: $F = .395$; d.f. = 1, 48; $p = .532$, $\eta^2 = .008$; STAI-State: $F = 2.3$; d.f. = 1, 48; $p = .136$, $\eta^2 = .046$). Furthermore, there was no significant interaction effect of time × treatment (time - × treatment effect: Visual Analog Scale *Anxiety*: $p = .119$, $\eta^2 = .038$; Visual Analog Scale *Physical Reactions*: $p = .620$, $\eta^2 = .014$; Visual Analog Scale *Avoidance*: $p = .457$, $\eta^2 = .018$; STAI-State: $p = .637$, $\eta^2 = .012$). Furthermore, t-tests for independent samples have been carried out for each single outcome variable at each time point. The cortisone group did not differ from the placebo group in any outcome variable at every time point (all $ps > .110$) except in the cortisol levels after administration of study medication (salivette 2–7; means shown in Table 1). Thus, whereas the TSST induced an increase in all fear dimensions in healthy subjects, cortisone treatment did not reduce fear, as previously shown in patients with social phobia (Soravia et al., 2006).

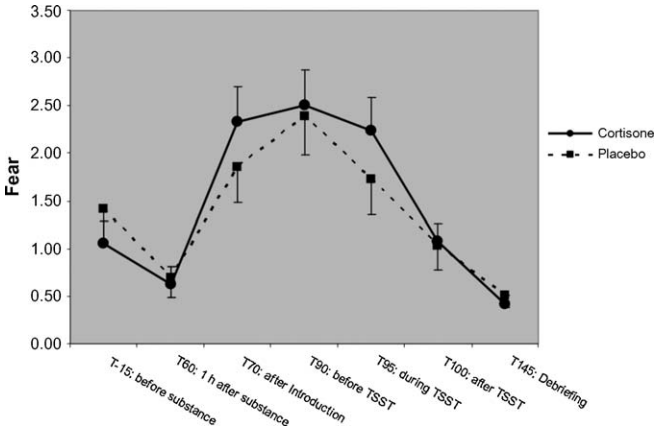

Fig. 2. Mean Scores of the Visual Analog Scale *Fear* in the subjects with cortisone or placebo treatment. Values are depicted as means ± SEM.

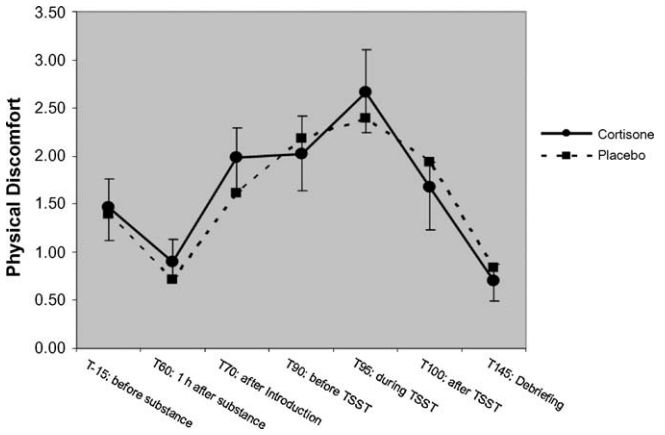

Fig. 3. Mean Scores of the Visual Analog Scale *Physical Discomfort* in the subjects with cortisone or placebo treatment. Values are depicted as means ± SEM.

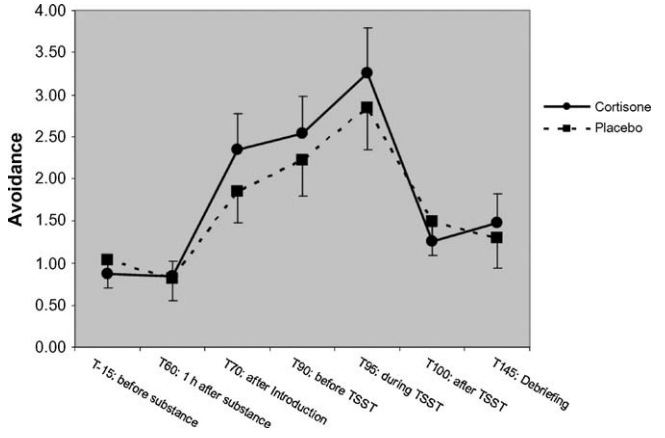

Fig. 4. Mean Scores of the Visual Analog Scale *Avoidance Behavior* in the subjects with cortisone or placebo treatment. Values are depicted as means ± SEM.

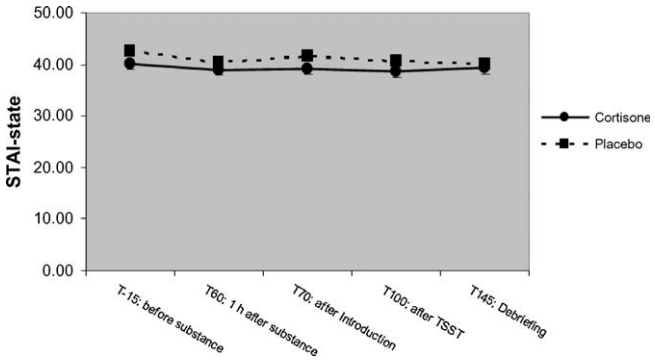

Fig. 5. Mean Scores of the STAI-State in the subjects with cortisone or placebo treatment. Values are depicted as means ± SEM.

3.4. Mood

Analyses of the three scales of the mood activity questionnaire did not reveal any significant treatment effects or interaction effects (treatment × time) (all $ps \geq .45$). But independent of the treatment, the stress exposure led to a change in mood over the time of the experiment with a significant decrease in the means of three scales termed elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness (time: all $ps < .001$).

3.5. Discussion

The major finding of the present study is that the administration of cortisone did not exert anxiolytic effects in healthy subjects exposed to social stress, although this stress situation robustly increased all dimensions of subjective fear (i.e. anxiety levels, physical discomfort and avoidance behavior). These fear dimensions have been previously found to be reduced by cortisone treatment in patients with social phobia (Soravia et al., 2006) using the same experimental design. Thus, these findings suggest that cortisone treatment does not have general anxiolytic effects, but rather has fear-reducing properties that are pronounced in conditions of pathological fear.

In the previous study in patients with phobia, the cortisone effect on subjective fear was on a significance level of $p = 0.004$ with 21 subjects (Soravia et al., 2006). In the present study in healthy subjects, cortisone did not affect subjective fear ($p = 0.5$), although the number of subjects was larger ($N = 50$). The comparison of these two studies, for which we used the same design and procedure, indicates that the present negative finding is unlikely the result of a lack of power.

A large body of evidence indicates that the administration of glucocorticoids leads to an inhibition of memory retrieval (de Quervain et al., 1998, 2000; Het et al., 2005) and that emotionally arousing information is especially sensitive to these retrieval-impairing effects of glucocorticoids (de Quervain et al., 2007; Kuhlmann et al., 2005). Using positron emission tomography in healthy humans, we found that acutely administered cortisone reduces blood flow in the medial temporal lobe (MTL) during memory retrieval, an effect that correlates with the degree of memory retrieval impairment (de Quervain et al., 2003). Furthermore, a recent functional magnetic resonance imaging study reported that glucocorticoids decrease MTL and prefrontal activation during declarative memory retrieval (Oei et al., 2007). In rats, systemic administration of glucocorticoids shortly before retention testing induced memory retrieval impairments for contextual memory (Roozendaal et al., 2004b), a task that depends on the MTL, and local infusions of a glucocorticoid receptor agonist into the hippocampus induced retrieval impairments comparable to those seen after systemic administration (Roozendaal et al., 2003). Together, these findings indicate that the MTL is involved in mediating the inhibitory effects of glucocorticoids on memory retrieval. Extensive evidence from studies in amnesic patients, human imaging studies, and lesion studies in animals indicates that the MTL is crucially involved in successful memory retrieval (Cabeza and Nyberg, 2000; Moser and Moser, 1998; Squire, 1992). Interestingly, a positron emission tomography study in patients with social phobia reported that the medial temporal lobe is activated by public speaking and that after successful psychotherapy or pharmacotherapy this brain region is less activated by the phobic stimulus (Furmark et al., 2002b). These findings suggest that the MTL activation is also involved in the retrieval of fear memory. Therefore, it is conceivable that glucocorticoids reduce pathological fear by inhibiting brain regions involved in the retrieval of fear memory, including the medial temporal lobe. Alternatively, or perhaps in addition to the glucocorticoid effects on memory retrieval, glucocorticoids might exert direct anxiolytic effects or modulate anxiety by affecting attention to negative information in healthy human subjects (Buchanan and Lovallo, 2001; Putman et al., 2007a,b). However, in these studies glucocorticoids did not affect subjective fear levels. Furthermore, it might be possible that negative feedback on corticotropin-releasing factor (CRF) release (Buchanan and Lovallo, 2001) may have been a reason for the observed fear-reducing effect of glucocorticoid administration in patients with phobia (Soravia et al., 2006). However, in the same study, the stress-induced release of cortisol in placebo-treated subjects correlated negatively with fear ratings, suggesting that the activation of the HPA-axis in the context of a phobic situation buffers fear symptoms and that therefore, reduced fear after glucocorticoid administration was unlikely the result of a negative feedback on corticotropin-releasing factor release.

In support of the view that glucocorticoids reduce pathological fear through an inhibition of fear memory retrieval (Soravia et al., 2006; de Quervain and Margraf, 2008), the present study did not find fear-reducing effects of glucocorticoids in healthy humans, in whom no pathological fear memory exists. This finding is in line with a recently published study showing no effects of cortisol administration on physiological responding to emotional memories in healthy young men (Tollenaar et al., 2009). Moreover, a comparison of the present results with those acquired in phobic patients (Soravia et al., 2006) reveals that cortisone reduced fear in phobic patients to the range of fear experienced by healthy subjects. Whereas in healthy subjects the TSST might elicit fear because this task is considered an actual stressful and unpleasant situation (Kirschbaum et al., 1993), it represents a phobic stimulus for patients with social phobia that almost invariably provokes retrieval of stimulus-associated fear memory leading to the fear response (Cuthbert et al., 2003; Foa and Kozak, 1986; Lang, 1985). Thus, as compared to fear of non-phobics, fear in patients with phobia might depend to a greater extent on fear acquired in the past. This might be the reason why glucocorticoids, which are known to reduce memory retrieval of emotional information, primarily affect fear in phobia. Alternatively, higher fear levels, as present in patients with phobia compared to non-phobic subjects, might be more susceptible to glucocorticoid effects.

Recent studies in healthy subjects found that the administration of glucocorticoids led to a better emotional state after a stress condition than placebo (Het and Wolf, 2007; Reuter, 2002). In the present study, we did not find such a mood effect as Het and Wolf did in their study. A major difference between the studies is that our sample consisted of male and female subjects, whereas the study by Het and Wolf investigated exclusively female subjects, who were using oral contraceptives and in Reuters study they investigated only male subjects. Further studies are needed to explore whether glucocorticoid effects on mood depend on gender

and/or oral contraceptives and whether glucocorticoid effects on mood and fear share common neurobiological mechanisms.

In sum, our findings show that glucocorticoids do not exert general anxiolytic effects in healthy subjects exposed to a fearful situation. These findings might further support the view that glucocorticoids reduce pathological fear through an inhibited retrieval of fear memory in patients with phobia. However, it is important to stress that the negative finding presented herein should not be over-interpreted. Clearly, more studies with larger samples are needed to investigate the effects of glucocorticoids on emotional processes in both men and women.

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