Research Article

GLUCOCORTICOIDS ENHANCE IN VIVO EXPOSURE-BASED THERAPY OF SPIDER PHOBIA

Leila M. Soravia, Ph.D.,[1]* Markus Heinrichs, Ph.D.,[2] Livia Winzeler, M.Sc.,[1] Melanie Fisler, M.Sc.,[1] Wolfgang Schmitt, M.D.,[1] Helge Horn, Ph.D.,[1] Thomas Dierks, Ph.D.,[1] Werner Strik, M.D.,[1] Stefan G. Hofmann, Ph.D.,[3] and Dominique J.-F. de Quervain, Ph.D.[4,5]

Background: *Preclinical and clinical studies indicate that the administration of glucocorticoids may promote fear extinction processes. In particular, it has been shown that glucocorticoids enhance virtual reality based exposure therapy of fear of heights. Here, we investigate whether glucocorticoids enhance the outcome of in vivo exposure-based group therapy of spider phobia.* **Methods:** *In a double blind, block-randomized, placebo-controlled, between-subject study design, 22 patients with specific phobia of spiders were treated with two sessions of in vivo exposure-based group therapy. Cortisol (20 mg) or placebo was orally administered 1 hr before each therapy session. Patients returned for a follow-up assessment one month after therapy.* **Results:** *Exposure-based group therapy led to a significant decrease in phobic symptoms as assessed with the Fear of Spiders Questionnaire (FSQ) from pretreatment to immediate posttreatment and to follow-up. The administration of cortisol to exposure therapy resulted in increased salivary cortisol concentrations and a significantly greater reduction in fear of spiders (FSQ) as compared to placebo at follow-up, but not immediately posttreatment. Furthermore, cortisol-treated patients reported significantly less anxiety during standardized exposure to living spiders at follow-up than placebo-treated subjects. Notably, groups did not differ in phobia-unrelated state-anxiety before and after the exposure sessions and at follow-up.* **Conclusions:** *These findings indicate that adding cortisol to in vivo exposure-based group therapy of spider phobia enhances treatment outcome. Depression and Anxiety 31:429–435, 2014.*

Key words: *Phobia; cortisol; glucocorticoids; exposure; group therapy; fear memory*

INTRODUCTION

Specific phobias are the most common of the anxiety disorders with an estimated lifetime prevalence of 11.3% in the American population.[1] Spider phobia is one of

[1]University Hospital of Psychiatry, University of Bern, Bern, Switzerland
[2]Department of Psychology, University of Freiburg, Freiburg, Germany
[3]Department of Psychology, Boston University, Boston, Massachusetts
[4]Division of Cognitive Neuroscience, Department of Psychology, University of Basel, Basel, Switzerland
[5]University of Basel, Psychiatric University Clinics, Basel, Switzerland

Contract grant sponsor: Swiss National Science Foundation; contract grant number: 32003B_124947 (L.S.); contract grant sponsor: Medical Faculty of the University of Bern; contract grant number: 520.10 (L.S.); contract grant sponsor: NIMH; contract grant numbers: MH-078308 and MH-081116 (S.H).

*Correspondence to: Leila Maria Soravia, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland. E-mail: soravia@puk.unibe.ch
Received for publication 10 June 2013; Revised 28 October 2013; Accepted 28 October 2013

DOI 10.1002/da.22219
Published online 21 November 2013 in Wiley Online Library (wileyonlinelibrary.com).

the most widespread forms of specific phobias.[2] Even though exposure-based interventions have been proven efficacious for the treatment of anxiety, more than one third of the patients do not respond to treatment, or achieve only partial remission of symptoms.[3–5] Core elements of cognitive-behavioral therapy are exposure to the feared object or situation, changes in maladaptive thinking, and extinction of fear responses.[6–8] Drugs with the potential to enhance extinction processes are thus promising candidates for enhancing exposure therapy, as it has been shown for d-cycloserine[9,10] and glucocorticoids.[11]

Results from animal and human studies show that the administration of the NMDAr partial agonist d-cycloserine prior to or soon after exposure trials accelerates and strengthens extinction of fear.[10,12,13] Comparable effects on memory processes have been found in studies with glucocorticoids. Glucocorticoids are stress hormones released from the adrenal cortex that affect memory processes.[14–16] Studies in animals and humans have shown that glucocorticoids can inhibit memory retrieval of emotionally arousing information and facilitate memory extinction processes.[11,16–19] Because anxiety disorders are characterized by vivid and excessive stimulus-associated fear memory, recent clinical studies investigated whether glucocorticoids can reduce the retrieval of aversive memories in patients with chronic PTSD,[20] and patients suffering from social phobia or spider phobia.[17] These studies found evidence that glucocorticoids reduce aversive memory retrieval and phobic fear symptoms during exposure and at follow up assessments. In patients with spider phobia, we have previously examined the effects of cortisol administration on subjective fear response without any concurrent therapy. Patients were repeatedly exposed to a spider photograph for 3 s, 1 h after cortisol (10 mg) or placebo administration.[17] This exposure time was too short to induce extinction per se, but cortisol led to a significantly greater reduction in fear than placebo. Therefore, in a recent study in patients with fear of heights, we examined whether adding glucocorticoids to a virtual-reality exposure therapy can promote fear extinction processes.[11] Adding cortisol to virtual-reality exposure therapy resulted in a significantly greater reduction in fear of heights as measured with the acrophobia questionnaire both at posttreatment and at follow-up, compared with placebo. In the present study, we aimed at investigating whether the administration of glucocorticoids has a beneficial effect when combined with an exposure-based short-term group therapy for spider phobia involving exposures to living spiders.

METHODS AND MATERIALS

PARTICIPANTS

Male and female subjects with spider phobia aged 20–60 were recruited via newspaper advertisement and flyers. Twenty-two subjects (five males, 17 females) who fulfilled the criteria for specific phobia for spiders were included in the study. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Specifically, we used a computer-based structured clinical interview (DIA-X),[21,22] which is based on the Composite International Diagnostic Interview (CIDI).[23] The German version[24] of the Spider Phobia Questionnaire (SPQ)[25] and the Fear of Spider Questionnaire (FSQ)[26] were further used to assess fear of spiders and demonstrate decrements of spider phobic symptoms achieved through behavioral therapy. Patients were excluded from the study if they met any of the following conditions that influence either cortisol level or the participation of psychotherapy in group format: history of head injury, acute, or chronic medical conditions, a recent history of systemic or oral glucocorticoid therapy, primary other psychiatric disorders than specific phobia for spiders, psychotropic drug treatment, smoking >15 cigarettes per day, neurological diseases, current drug or alcohol abuse, pregnancy and the use of hormonal contraceptives, current behavioral therapy.

After providing a complete description of the study to the subjects, written informed consent was obtained. The study was approved by the ethics committee of the Canton of Bern, Switzerland (Nr. 161/07) in accordance with the principles of the Declaration of Helsinki[27] and the Swiss agency for the authorization and supervision of therapeutic products (Swissmedic). After an initial telephone screening of 119 subjects who expressed interest in the study (see flow figure according to the CONSORT rules in the supplements). Ninety-four subjects had to be excluded after the telephone screening because of the use of hormonal contraceptives and smoking more than 15 cigarettes per day. Twenty-five patients remained eligible and signed informed consent. After the diagnostic interview two patients refused to participate in the study. Of the 23 eligible patients who were randomly assigned to the double blind, placebo-controlled design, one had to be excluded from analysis because the person withdrew after the first therapy session. A block randomization was applied to minimize possible disruptive factors of the group therapy (e.g. effects of group-cohesion, psychotherapist). Block randomization and blinding was conducted by the pharmacy of the University Hospital of Berne. Hence, half of the patients of one psychotherapy group received the active medication (hydrocortisone, see Procedure), whereas the other half received a placebo. Patients received the same medication at session one and two. Twenty-two patients (cortisol group: 11, who received exposure therapy plus hydrocortisone, mean age, 33.1 ± 9.6 and placebo group: 11 who received exposure therapy plus placebo, mean age, 30.5 ± 12.1) completed the two-session treatment with the 1-month follow-up assessment. All subjects received 100 Swiss francs as a compensation for their participation.

PROCEDURE

The study took place at the laboratories of the University Hospital of Psychiatry of Bern, Switzerland. The study consisted of three consecutive phases: (i) pretreatment assessment consisted of an initial telephone screening, followed by questionnaires and a diagnostic interview to assess symptoms and clarify study eligibility before treatment, (ii) treatment consisted of two exposure-based group therapy sessions within 2 weeks, and (iii) follow-up assessment 28–32 days after the last treatment session consisting of a standardized exposure. At the two treatment sessions either 20 mg of hydrocortisone (two tablets of 10 mg each of hydrocortisone; Hydrocortone®, MSD, Merck Sharp & Dohme-Chibret AG, Switzerland) or placebo (Galepharm, Switzerland) was orally administered 1 h before the exposure procedure in order for the medication to be absorbed. Dosage and timing was based on our previous studies: 20 mg of hydrocortisone was used in the study with acrophobia[28] and is equivalent to 25 mg of cortisone used in the study with social phobia[17]. In the studies with several administrations per weak, we used a lower dose of 10 mg of hydrocortisone.[17,20] Saliva samples were repeatedly collected to check and document the

effectiveness of the cortisone administration. Hydrocortisone and the placebo were encapsulated in identically looking capsules. The preparation of study medication, blinding, and randomization list was performed by the Pharmacy of the University Hospital Bern according to Good Clinical Practice standards (GCP).

EXPOSURE TREATMENTS AND FOLLOW-UP ASSESSMENT

The exposure treatment was conducted in groups of five to six patients (one group with five patients; three groups with six patients) led by one licensed psychotherapist and one cotherapist in 2 weekly 2.5-hr sessions between 6 PM and 9 PM. The exposure-based group therapy manual was derived from the treatment manual "Specific Phobias" from A. Hamm[29] and the treatment manual "Exposure-Based Cognitive-Behavioral Therapy for Individuals with Anxiety Disorders" from S. Hofmann.[30] The first hour of both therapy sessions involved psychoeducation about spider phobia and its treatment with exposure therapy, fear circuits, avoidance behavior, and group rules. After a 5-min break, 1.5 hr of exposure to differently sized real spiders followed. The exposures included looking at the spiders in the glass, touching the spider in the glass with a pen, touching the spider in the glass with a finger, catching the spider with a glass, and letting the spider walk over one's hand. Patients absolved each exposure under the direct guidance of the psychotherapist. Both sessions ended with feedback, in which every patient reported his own personal experience during the therapy session.

One month after the last therapy session each patient underwent a standardized exposure procedure and filled out questionnaires to evaluate therapy outcome. The follow-up assessment included the rating of subjective fear while viewing 20 pictures of spiders on the computer and a standardized exposure to a real spider. During the standardized exposure patients had to rate their subjective fear, physical discomfort, and avoidance behavior (i) before entering the room of the spider, (ii) when looking at the spider in the glass and finally (iii) when touching the spider.

SALIVA MEASUREMENTS

Three saliva samples were collected using the Salivette (Sarstedt Inc., Rommelsdorf, Germany) during each therapy session to ascertain the metabolization of the glucocorticoid into endogenous cortisol. A baseline saliva sample was taken immediately before substance administration, 1 hr after the administration of the study drug and at the end of the exposure session (2.5 hr after substance administration).

After each experimental session, samples were stored at -20°C. For biochemical analyses of free cortisol concentration, saliva samples were thawed and spun at 3,000 revolutions per minute for 10 min to obtain 0.5–1.0 ml of clear saliva with low viscosity. Salivary cortisol concentrations were determined by a commercially available chemiluminescence immunoassay (CLIA; IBL, Hamburg, Germany). Inter- and intraassay coefficients of variation were both below 8%.

SELF-REPORT MEASURES

Fear of Spiders. The German version[24] of the SPQ[25] and the FSQ[26] were used to assess the fear of spiders. The FSQ was administered at the diagnostic phase, before treatment session 1, after treatment session 2 and at 1-month follow-up assessment. The SPQ was administered at the pretreatment and the follow-up assessments.

Trait Anxiety and Depression. Trait anxiety and depressive symptoms were assessed at pretreatment assessment using the German version[31] of the Spielberger State-Trait Anxiety Inventory (STAI)[32] and the German version of the Beck depression inventory (BDI).[33]

State Anxiety. During the treatment sessions, state anxiety was measured before substance administration, before exposure, and after exposure procedure using the German version[31] of the Spielberger State Anxiety Inventory (STAI-state)[32] that measures subjective anxiety at the moment of assessment. Additionally, subjects rated their subjective actual discomfort in the dimensions anxiety, physical reaction, and avoidance using a visual analog scale from 0 (no symptoms) to 10 (maximal symptoms). During the follow-up assessment patients rated the perceived fear while viewing pictures of spiders and after each of the three standardized follow-up exposures on the same visual analog scales as used during the treatment sessions.

Assessment of Blinding. Patients were asked after each treatment session whether they believed they were assigned to active medication or placebo. Furthermore, they were asked to report any psychological or physiological side effects of the study drug after each exposure session.

DATA ANALYSIS. Data were entered by blinded research assistants into SPSS version 19.0 statistical software package. Group differences in demographic and clinical characteristics, and state anxiety during treatment sessions were analyzed with unpaired *t*-tests. Effects of cortisone administration on salivary cortisol concentrations and fear of spider symptoms were analyzed with two-way repeated measures ANOVAs with treatment as the between-subject factor and time points as the within-subject factor. Unpaired *t*-tests were used to analyze treatment effects at a certain time point. The controlled effect size (Cohen's d) was calculated for significant variables. Treatment credibility was analyzed with chi-square tests. All tests were two-tailed and a probability of < 0.05 was considered statistically significant. All variables were normally distributed (Kolmogorov–Smirnov test: $P > 0.1$, for all variables).

RESULTS

The two groups, consisting of 11 patients (four males, seven females) in the cortisol group and 11 patients (one males, 10 females) in the placebo group, did not differ significantly in any demographic, clinical characteristics, or smoking status or in any of the baseline measurements (Supporting Information Table S1). Neither were there group differences regarding irregular cycling (Chi-square $_{(1)} = .505$; $P = 0.477$). All female subjects were tested between 12 and 34 days after the end of the last menstrual period (within the luteal phase). During the group therapy sessions, subjects who had received cortisol had significantly higher salivary cortisol concentration before ($P \leq 0.003$) and after ($P < 0.001$) the exposure procedure than subjects who had received placebo (Fig. 1, Supporting Information Table S2). Inclusion of smoking as a covariate did not change the results concerning the effects of cortisone administration on cortisol levels (Session 1: $F = 39.7$; $df = 1, 19$; $P < 0.001$; Session 2: $F = 111.44$; $df = 1, 19$; $P < 0.001$). At treatment session 1, subjects treated with glucocorticoids showed slightly higher baseline salivary cortisol levels before substance administration than the placebo group (Cortisol group: 8.9 ± 1.3; Placebo group: 5.1 ± 0.5; $P = 0.031$). However, there was no group difference in baseline salivary cortisol concentration on the second treatment session ($P = 0.26$). Groups did not differ in

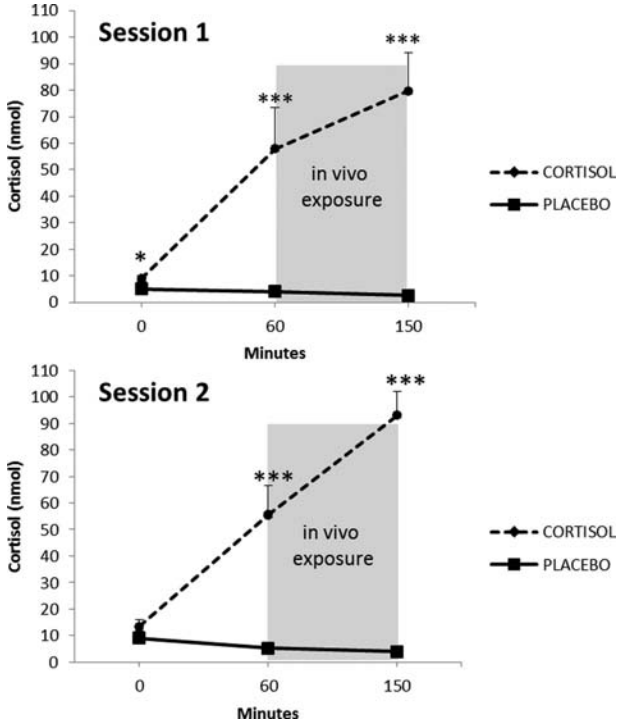

Figure 1. Salivary cortisol levels (nmol/l) during treatment session 1 and 2. The administration of hydrocortisone (20 mg) led to significantly higher cortisol levels in the cortisol group as compared to the placebo group throughout exposure procedure (between 60 and 150 min) at treatment session 1 and 2 ($P < 0.001$).

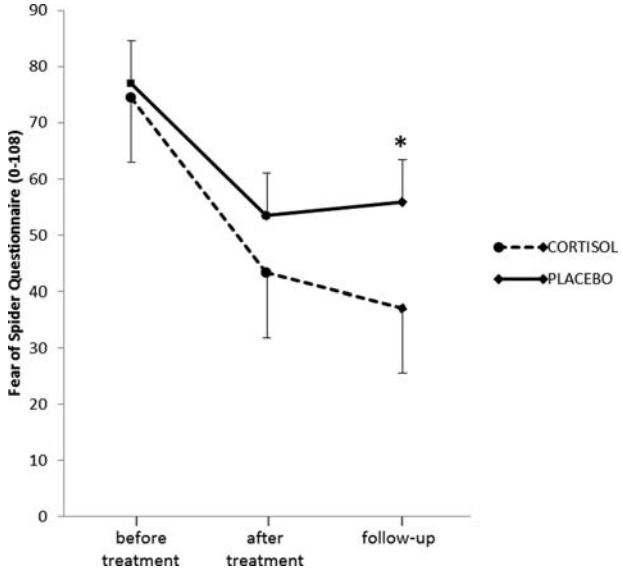

Figure 2. Administration of cortisol to an exposure-based group therapy resulted in reduction of self-reported fear of spiders (measured with the fear of spider questionnaire, range 0–108) at follow-up assessment. Cortisol was administered 1 h before the exposure sessions in both group therapy sessions. Values are depicted as mean ± SEM. Astericks indicate significant differences at a certain time point, * $P < 0.05$.

baseline cortisol levels at follow-up before and after exposure (Supporting Information Table S2).

EFFECTS OF EXPOSURE-BASED GROUP THERAPY

Analysis of the spider phobic symptoms over time showed a significant overall reduction of fear as measured with the FSQ from pretreatment (75.8 ± 2.4; mean ± SEM) to posttreatment (48.4 ± 3.3; $F_{1,21} = 52.7$; $P < 0.001$; Cohen's $d = 2.02$) and follow-up assessment in both groups (46.5 ± 4.3; $F_{1,21} = 35.6$; $P < 0.001$; Cohen's $d = 1.79$). No significant fear symptom change was observed from posttreatment to follow-up ($F_{1,21} = 0.5$; $P = 0.495$; Cohen's $d = 0.11$). Spider phobic symptoms measured with the SPQ revealed a significant symptom reduction from pretreatment (20.8 ± 1.0; mean ± SEM) to follow-up (15.2 ± 0.8; $F_{1,21} = 27.4$; $P < 0.001$; Cohen's $d = 1.33$).

EFFECTS OF CORTISOL

Cortisol-treated participants showed a significantly greater reduction in spider phobic symptoms as measured with the FSQ over the sessions as compared to placebo-treated patients (Fig. 2; repeated-measured ANOVA, $F_{1,19} = 4.52$; $P = 0.047$/pretreatment measurement as covariate). Whereas the cortisol group did not significantly differ from the placebo group in spider phobic symptoms at posttreatment (cortisol, 43.3 ± 3.4; placebo, 53.5 ± 5.3; $F_{1,20} = 2.61$; $P \geq 0.1$; Cohen's $d = 0.69$), it showed significantly less spider phobic symptoms compared to the placebo group at follow-up assessment (cortisol group: 37.1 ± 5.5; placebo group: 56.0 ± 5.5; $F_{1,20} = 5.89$; $P = 0.025$; Cohen's $d = 1.04$). Moreover, cortisol-treated patients showed significantly fewer symptoms measured with the SPQ at follow-up as compared to placebo treated patients (cortisol group: 13.5 ± 1.0; placebo group: 16.95 ± 1.1; $F_{1,20} = 5.27$; $P = 0.033$; Cohen's $d = 0.98$). Participants' sex did not influence the cortisol effect (interaction sex X drug, FSQ: $P = 0.89$; SPQ: $P > 0.8$). Cortisol treatment did not reduce general anxiety (STAI-state, visual analog scales) during the group therapy sessions (Supporting Information Table S2), nor did the groups differ in state-anxiety before and after the exposure procedure at follow-up (Supporting Information Table S2).

During the standardized follow-up assessment cortisol-treated patients reported significantly less subjective fear after viewing 20 pictures of spiders as compared to the placebo group ($t_{20} = -3.6$; $P = 0.002$; Cohen's $d = -1.61$). The groups did not differ in their level of disgust or arousal during this task (Table 1). The second exposure task regarding anticipatory anxiety included the rating of state anxiety, physical discomfort, and avoidance behavior before entering the room with a spider. Cortisol-treated subjects showed less physical discomfort ($t_{20} = -2.4$; $P = 0.027$; Cohen's $d = -1.07$)

TABLE 1. Fear ratings at follow-up assessment

	Placebo group	Cortisol group	Significance, *P*
Exp. 1: Pictures of spiders			
Fear	50.5 ± 4.7	26.7 ± 4.7	0.006
Disgust	47.3 ± 8.0	36.3 ± 5.9	0.828
Arousal	28.4 ± 2.9	27.4 ± 5.6	1.00
Exp. 2: Anticipatory anxiety to in vivo exposure			
Fear	32.3 ± 3.8	20.6 ± 5.1	0.243
Physical discomfort	33.5 ± 2.3	20.5 ± 4.9	0.081
Avoidance	25.6 ± 5.6	15.2 ± 5.1	0.561
Exp. 3: Looking at the spider in a glass			
Fear	51.2 ± 5.1	16.1 ± 2.6	<0.001
Physical discomfort	49.0 ± 7.2	17.3 ± 2.7	0.003
Avoidance	42.5 ± 6.9	15.2 ± 5.2	0.015
Exp. 4: Touching the spider			
Fear	44.6 ± 7.0	11.9 ± 2.6	<0.001
Physical discomfort	42.4 ± 6.3	18.4 ± 3.3	0.012
Avoidance	19.2 ± 5.4	15.1 ± 6.4	1.00

Anxiety ratings measured with visual analog scales at follow-up assessment four weeks after cessation of exposure-based group therapy. Follow-up assessment consisted of four standardized exposure procedures. Exp.: standardized exposure. Data are presented as mean ± SEM. *P*-values are corrected for multiple comparisons (Bonferroni correction).

and a trend toward lower state anxiety ($t_{20} = -1.8$; $P = 0.081$; Cohen's $d = -0.80$) before confronting a spider. Groups did not differ in their wish to leave the situation and avoid the confrontation with the spider (Table 1). However, at the third exposure task when exposed to the spider in a glass, cortisol-treated patients reported significantly less subjective fear, less physical discomfort, and less avoidance behavior ($P \leq 0.005$). The cortisol group reported less subjective fear and physical discomfort ($P \leq 0.004$) at the fourth exposure task when they were asked to touch the spider. There was no treatment-related difference in avoidance behavior during this task ($P \geq 0.6$). None of the patients reported adverse side effects due to drug administration, nor was there any group difference in the patients' beliefs in having received the active medication or placebo at session 1 and 2 ($P > 0.3$).

DISCUSSION

The findings of the present study indicate that adding glucocorticoids to in vivo exposure-based group therapy enhances treatment outcome in patients with spider phobia. Specifically, patients receiving cortisol during treatment showed a significantly greater reduction in spider phobic symptoms as measured with the spider phobia questionnaires FSQ and SPQ at follow-up when compared to placebo-treated patients. Whereas the cortisol-induced reduction of spider phobic symptoms (FSQ) was not significant right after treatment session two, this reduction was significant at follow-up. This might be because the glucocorticoid effects on consolidation processes—including consolidation of extinction memory—do not occur right after training.[28] Furthermore, patients in the cortisol group reported significantly less subjective fear and less physical discomfort when exposed to a living spider at follow-up assessment. Notably, groups did not differ in phobia-unrelated state-anxiety before and after the exposure sessions and at follow-up. Interestingly, placebo-treated patients did not show stress-induced release of cortisol by exposure sessions. Several studies in humans indicate that variables like novelty, controllability, predictability, ambiguity, anticipation, and social factors play another important role in the release of an acute stress response.[34–37] A meta-analysis reviewing 208 laboratory stress tests shows that tasks containing uncontrollable and social-evaluative elements are associated with the largest cortisol and adrenocorticotropin hormone changes and show the longest times of recovery.[38] However, in our study, patients were familiar to the environment of the lab, well informed about the exposure procedure (predictability), were able to stop the exposure at any time (controllability) and were not in a socio-evaluative setting which might explain the absence of cortisol increase during exposure sessions. Therefore the present procedure did either not meet the criteria for HPA activation, or patients with spider phobia tend to show a dampened cortisol response upon confrontation with a phobic stimulus. In line with the previous studies applying glucocorticoids, no side-effects were reported by the patients neither could patients tell whether they received the active medication or placebo.[11,17,20,39]

A large body of studies in animals and humans demonstrates that glucocorticoids enhance the consolidation of new information.[18,19,40] Furthermore, it has been shown that glucocorticoids impair memory retrieval, especially of emotionally arousing information,[14,16,41,42] In phobic individuals, exposure to a phobic stimulus almost invariably provokes retrieval of stimulus-associated fear memory, which leads to the fear response.[6–8,11,17,43–46]. It has further been shown that the oral administration of 25 mg of cortisone reduced phobic fear in a social-evaluative stress test (TSST) in individuals with social phobia.[17] Furthermore, the stress-induced release of cortisol in placebo-treated patients correlated negatively with the fear ratings, suggesting that the release of stress hormones in a phobic situation may buffer fear symptoms. In a study with spider phobic patients it has been shown that repeated oral administration of hydrocortisone (10 mg), but not placebo, one hour before the exposure to spider photographs caused a progressive reduction of stimulus-induced fear.[17] This effect was maintained even in further exposure to the stimulus 2 days after the last cortisol administration suggesting that cortisol also facilitates the extinction of phobic fear.

Based on the known effects on memory processes, glucocorticoids may facilitate the extinction of a fear memory trace in two ways: (i), because of the glucocorticoid-induced reduction of memory retrieval, an aversive cue is no longer followed by the usual, full-blown retrieval of

fear memory and related clinical symptoms but, instead, becomes associated with a less aversive experience, which is stored as extinction memory; (ii), because glucocorticoids are known to enhance memory consolidation of new information, it is possible that glucocorticoids also enhance the storage of corrective experiences (i.e. extinction memory).[16] This notion is supported by recent animal studies showing that postretrieval administration of glucocorticoids is able to enhance the consolidation of extinction memory.[47,48]

The mnemonic actions of glucocorticoids seem to be especially suited for the treatment of fear memory. By inhibiting memory retrieval, glucocorticoids may reduce the reactivation of the fear-memory network resulting in less fear upon confrontation with a phobic stimulus. Simultaneously, glucocorticoids may promote the storage of corrective experiences through a facilitating effect on consolidation of extinction memory.[16] However, these first studies did not examine the effect of glucocorticoids on subjective fear when combined with an exposure intervention. This question was examined in a study that investigated whether the administration of cortisol (20 mg) might be useful in enhancing virtual reality exposure therapy for patients with specific phobia for heights.[11] The results showed that the combination of glucocorticoid administration and virtual reality (VR) therapy showed greater symptom reduction compared to VR and placebo treatment. This effect was maintained at follow up, 1 month after treatment discontinuation when patients were exposed to a virtual height situation. Even though the virtual-exposure procedure used in that study is not comparable to real-life situations, the findings suggested that the administration of cortisol is suited to enhancing extinction-based psychotherapy. The objective of the present study examined this critical remaining question, which has important implications for clinical practice. The findings indeed indicate that adding cortisol to in vivo exposure-based group therapy of patients with spider phobia enhances treatment outcome when tested by a direct confrontation of the feared object. Therefore, it might be possible to enhance standard exposure therapy with cortisol.

Some limitations have to be considered. The exclusion of female subjects with hormonal contraceptives led to a quite small sample size. Randomization further revealed that there is only one male subject in the cortisol group while there are four placebo treated male subjects. The present data were obtained with a dose of 20 mg of cortisol. Cortisol effects with other doses have to be tested in further studies. Future studies are also needed to address the questions of optimal timing of cortisol administration, and to investigate the synergistic or antagonistic potential of a combined application of cortisol with other drugs.

Acknowledgments. We thank Joëlle Witmer, Basil Preisig, and Yvonne Renevey for excellent research assistance.

REFERENCES

1. Magee WJ, Eaton WW, Wittchen HU, et al. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry 1996;53:159–168.
2. Bourdon KH, Boyd JH, Rae DS, et al. Gender differences in phobias: results of the ECA community survey. J Anxiety Disorders 1988;2:227–241.
3. Hofmann SG, Smits JAJ. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry 2008;69:621–632.
4. Cuthbert BN. Social anxiety disorder: trends and translational research. Biol Psychiatry 2002;51:4–10.
5. Heimberg RG. Cognitive-behavioral therapy for social anxiety disorder: current status and future directions. Biol Psychiatry 2002;51:101–108.
6. Bentz D, Michael T, de Quervain DJF, et al. Enhancing exposure therapy for anxiety disorders with glucocorticoids: from basic mechanisms of emotional learning to clinical applications. J Anxiety Disorders 2010;24:223–230.
7. Hermans D, Craske MG, Mineka S, et al. Extinction in human fear conditioning. Biol Psychiatry 2006;60:361–368.
8. McNally RJ. Mechanisms of exposure therapy: how neuroscience can improve psychological treatments for anxiety disorders. Clin Psychol Rev 2007;27:750–759.
9. Hofmann SG, Meuret AE, Smits JAJ, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. Arch Gen Psychiatry 2006;63:298–304.
10. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry 2004;61:1136–1144.
11. de Quervain DJ-F, Bentz D, Michael T, et al. Glucocorticoids enhance extinction-based psychotherapy. Proc Natl Acad Sci 2011;108:6621–6625.
12. Hofmann S, Suvak M. Treatment attrition during group therapy for social phobia. J Anxiety Disord 2006;20:961–972.
13. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 2007;33:56–72.
14. De Quervain DJ-F, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 1998;394:787–790.
15. de Quervain DJF, Roozendaal B, Müller-Spahn F, et al. Cortisol impairs free recall of long-term declarative memory in healthy human subjects. Psychoneuroendocrinology 2000;25(Supplement 1):S51.
16. de Quervain DJF, Aerni A, Schelling G, et al. Glucocorticoids and the regulation of memory in health and disease. Frontiers Neuroendocrinol 2009;30:358–370.
17. Soravia LM, Heinrichs M, Aerni A, et al. Glucocorticoids reduce phobic fear in humans. Proc Natl Acad Sci 2006;103:5585–5590.
18. Roozendaal B. Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 2000;25:213–238.
19. Buchanan TW, Lovallo WR. Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 2001;26:307–317.
20. Aerni A, Traber R, Hock C, et al. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiatry 2004;161:1488–1490.
21. Essau CA, Wittchen HU, Pfister H. DIA-X-Interview. Diagnostica 1999;45:163–164.
22. Wittchen HU, Pfister H. Instruktionsmanual zur Durchführung von DIA-X-Interviews. Frankfurt: Swets Test Services; 1997.
23. Rubio-Stipec M, Bravo M. The composite international diagnostic interview (CIDI): an epidemiologic instrument suitable for

using in conjunction with different diagnostic systems in different cultures. Acta Psiquiatr Psicol Am Lat 1991;37:191–204.
24. Rinck M, Bundschuh S, Engler S, et al. Reliability and validity of german versions of three instruments measuring fear of spider. Diagnostica 2002;48:141–149.
25. Watts FN, Sharrock R. Questionnaire dimensions of spider phobia. Behav Res Ther 1984;22:575–580.
26. Szymanski J, O'Donohue W. Fear of spider questionnaire. J Behav Ther Exp Psychiatry 1995;26:31–34.
27. Rickham P. Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. Br Med J 1964;2:177.
28. de Quervain DJ-F, Bentz D, Michael T, et al. Glucocorticoids enhance extinction-based psychotherapy. Proc Natl Acad Sci 2011;108:6621–6625.
29. Hamm A, Spezifische Phobien. Göttingen: Hogrefe; 1997.
30. Hofmann SG, Otto MW. Cognitive-Behavior Therapy of Social Anxiety Disorder: Evidence-based and Disorder Specific Treatment Techniques. New York, NY: Routledge; 2008.
31. Laux L. ed. State-Trait-Angstinventar theoretische Grundlagen und Handanweisung. Beltz Testgesellschaft: Weinheim; 1981.
32. Spielberger CD, Gorsuch RC, Lushene RE. Manual for the State-trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1970.
33. Hautzinger M, Worall H, Keller F. Beck Depressionsinventar (BDI). Bern: Huber; 1994.
34. Kirschbaum C, Hellhammer D. Psychoendokrinologie und Psychoimmunologie. In: Enzyklopädie der Psychologie, C. Kirschbaum, Hellhammer, D, editors. Hogrefe: Göttingen; 1999.
35. Wolf OT Stress and memory in humans: twelve years of progress? Brain Res 2009;1293:142–154.
36. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28:79–81.
37. Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. Neurosci Biobehav Rev 2010;35:91–96.
38. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull 2004;130:355–391.
39. Soravia LM, de Quervain DJF, Heinrichs M. Glucocorticoids do not reduce subjective fear in healthy subjects exposed to social stress. Biol Psychol 2009;81:184–188.
40. McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 2002;12:205–210.
41. De Quervain DJ-F, Roozendaal B, Nitsch RM, et al. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 2000;3:313–314.
42. Kuhlmann S, Kirschbaum C, Wolf OT. Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. Neurobiol Learning Memory 2005;83:158–162.
43. Cuthbert BN, Lang PJ, Strauss C, et al. The psychophysiology of anxiety disorder: fear memory imagery. Psychophysiology 2003;40:407–422.
44. Lang P. The cognitive psychophysiology of emotion: fear and anxiety. In: Tuma AH, editor. Anxiety and the Anxiety Disorders. Hillsdale, NJ: Erlbaum; 1985:131–170.
45. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective informatione. Psychol Bull 1986;99:20–35.
46. Alpers GW, Abelson JL, Wilhelm FH, et al. Salivary cortisol response during exposure treatment in driving phobics. Psychosom Med 2003;65(4):679–687.
47. Cai W-H, Blundell J, Han J, et al. Postreactivation glucocorticoids impair recall of established fear memory. J Neurosci 2006;26:9560–9566.
48. Abrari K, Rashidy-Pour A, Semnanian S, et al. Post-training administration of corticosterone enhances consolidation of contextual fear memory and hippocampal long-term potentiation in rats. Neurobiol Learning Memory 2009;91:260–265.