

Glucocorticoids reduce phobic fear in humans

Leila M. Soravia*, Markus Heinrichs*, Amanda Aerni†, Caroline Maroni†, Gustav Schelling‡, Ulrike Ehler*, Benno Roozendaal§, and Dominique J.-F. de Quervain*†¶

*Institute of Psychology, Department of Clinical Psychology and Psychotherapy, University of Zürich, Zürichbergstrasse 43, CH-8044 Zürich, Switzerland; †Division of Psychiatry Research, University of Zürich, Lenggstrasse 31, CH-8032 Zürich, Switzerland; ‡Department of Anaesthesiology, Ludwig-Maximilians University, 81377 Munich, Germany; and §Center for the Neurobiology of Learning and Memory, Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-3800

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Phobias are characterized by excessive fear, cued by the presence or anticipation of a fearful situation. Whereas it is well established that glucocorticoids are released in fearful situations, it is not known whether these hormones, in turn, modulate perceived fear. As extensive evidence indicates that elevated glucocorticoid levels impair the retrieval of emotionally arousing information, they might also inhibit retrieval of fear memory associated with phobia and, thereby, reduce phobic fear. Here, we investigated whether acutely administered glucocorticoids reduced phobic fear in two double-blind, placebo-controlled studies in 40 subjects with social phobia and 20 subjects with spider phobia. In the social phobia study, cortisone (25 mg) administered orally 1 h before a socio-evaluative stressor significantly reduced self-reported fear during the anticipation, exposure, and recovery phase of the stressor. Moreover, the stress-induced release of cortisol in placebo-treated subjects correlated negatively with fear ratings, suggesting that endogenously released cortisol in the context of a phobic situation buffers fear symptoms. In the spider phobia study, repeated oral administration of cortisol (10 mg), but not placebo, 1 h before exposure to a spider photograph induced a progressive reduction of stimulus-induced fear. This effect was maintained when subjects were exposed to the stimulus again 2 days after the last cortisol administration, suggesting that cortisol may also have facilitated the extinction of phobic fear. Cortisol treatment did not reduce general, phobia-unrelated anxiety. In conclusion, the present findings in two distinct types of phobias indicate that glucocorticoid administration reduces phobic fear.

cortisol | memory | cortisone | extinction

Phobic disorders are characterized by marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (1, 2). Exposure to a phobic stimulus almost invariably provokes retrieval of stimulus-associated fear memory (3), which may be innate or acquired by conditioning (4). In addition, phobic individuals tend to construct highly negative images of a phobic situation, which substantially contributes to anticipatory anxiety and negative postevent 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 (5, 6).

Although it is well established that phobic stimuli trigger the release of cortisol (7–10), it has not been investigated whether cortisol feeds back to influence fear symptoms. In contrast to the enhancing effects of glucocorticoids on memory consolidation (11), we have shown previously that pretest administration of glucocorticoids inhibits the retrieval of previously acquired information in animals (12) and humans (13). The impairing effect of glucocorticoid administration on memory retrieval is a highly consistent finding (14–18), and recent evidence indicates that emotionally arousing information is especially sensitive to the retrieval-impairing effects of glucocorticoids (19, 20). Furthermore, we reported findings indicating that low-dose cortisol treatment reduces retrieval of traumatic memories in posttraumatic stress disorder (21). Such findings suggest that glucocor-

ticoids also might inhibit retrieval of fear memory in phobia and, thereby, reduce stimulus-induced fear. In the present study, we investigated whether glucocorticoid administration affected fear symptoms in two double-blind, placebo-controlled studies in subjects with social phobia and spider phobia.

Subjects with social phobia were exposed to the Trier Social Stress Test (TSST), a standardized socio-evaluative stressor consisting of an unprepared speech and mental arithmetic task performed in front of an audience (22). The TSST represents a strong phobic stimulus for these patients because the essential feature of social phobia is the fear of social or performance situations when patients feel they are under scrutiny by others and fear doing something embarrassing or humiliating (2). Cortisone (25 mg) or placebo was administered orally 1 h before exposure to the social stressor, and subjective fear, heart-rate reactivity and salivary cortisol levels were measured repeatedly (Fig. 1A). Furthermore, we investigated the effect of cortisone administration on fear symptoms in socially phobic subjects who were not exposed to the social stressor.

Subjects with spider phobia were exposed to a phobic stimulus consisting of a photograph of a spider (see Fig. 3A) on six different occasions distributed over a period of 2 weeks. Cortisol (10 mg) or placebo was administered orally 1 h before the presentation of the stimulus on sessions 2–5, and subjective fear induced by the phobic stimulus was measured. On sessions 1 and 6 there was no drug treatment before stimulus presentation to assess baseline symptoms and to examine whether fear ratings had returned to baseline after cessation of the treatment, respectively.

Results

Social Phobia Study. Social stress condition. The two groups, consisting of 9 male patients in the cortisone group and 12 male patients in the placebo group, did not differ significantly in demographic and clinical characteristics or in any of the baseline measurements on the day of experiment (Table 2, which is published as supporting information on the PNAS web site). The administration of cortisone significantly increased salivary cortisol levels throughout the experiment as compared with those of the placebo group (repeated-measures ANOVA, $F = 12.18$; $df = 1, 18$; $P = 0.003$). In the placebo group, there was a significant stress-induced elevation of cortisol levels when comparing pre-TSST levels with those immediately or 45 min after the TSST (paired t tests; $P \leq 0.002$).

Cortisone treatment significantly reduced self-reported fear during the anticipation, stress exposure, and recovery phase of the TSST, as assessed with a visual analog scale (repeated-measures ANOVA, $F = 10.97$; $df = 1, 17$; $P = 0.004$; area under

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Abbreviations: MTL, medial temporal lobe; TSST, Trier Social Stress Test.

¶To whom correspondence should be addressed. E-mail: quervain@bli.unizh.ch.

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salivary cortisol levels comparable to those found in the first experiment (repeated-measures ANOVA, $F = 17.59$; $df = 1, 16$; $P < 0.001$; as compared to placebo). Baseline fear ratings were low (placebo, 1.1 ± 0.4 ; cortisone, 1.0 ± 0.4), and cortisone treatment did not reduce self-reported fear during the remaining resting period (T60–T145, repeated-measures ANOVA, $F = 3.86$; $df = 1, 16$; $P = 0.07$). The area under the curve analysis did also not reveal a treatment-related difference ($F = 0.57$; $df = 1, 17$; $P = 0.5$). Also, for all other measures of fear-related symptoms or mood, there were no significant treatment effects (data not shown).

Spider Phobia Study. The two groups, consisting of 10 patients (2 males and 8 females) in the cortisol group and 10 patients (2 males and 8 females) in the placebo group, did not differ significantly in demographic or clinical characteristics (Table 4, which is published as supporting information on the PNAS web site). On the sessions with a pharmacological treatment (sessions 2–5), subjects who had received cortisol 1 h before stimulus exposure had significantly higher salivary cortisol concentrations during stimulus presentation compared with subjects administered placebo ($P \leq 0.014$; Table 5, which is published as supporting information on the PNAS web site). On the sessions without pharmacological treatment (sessions 1 and 6), salivary cortisol concentrations did not differ between the two groups at the time of stimulus presentation ($P \geq 0.9$).

Cortisol treatment significantly reduced stimulus-induced fear over the sessions as compared with placebo treatment, as measured with a visual analog scale (repeated-measures ANOVA, $F = 6.73$; $df = 1, 17$; $P = 0.02$). Within the placebo group, there was no significant session effect on stimulus-induced fear (repeated-measures ANOVA, $F = 0.79$; $df = 3.2, 28$; $P = 0.5$; Fig. 3B), indicating that repeated exposures to the phobic stimulus did not result in an extinction of fear symptoms during the course of the experiment. In contrast, there was a significant session effect on stimulus-induced fear in the cortisol group (repeated-measures ANOVA, $F = 9.33$; $df = 3, 27$; $P < 0.001$; Fig. 3B). Specifically, fear ratings on all sessions with cortisol treatment (sessions 2–5) were significantly lower than baseline ratings on session 1 (paired t tests; $P < 0.05$ for all comparisons). After the fourth cortisol administration (session 5), stimulus-induced fear was reduced by 45% as compared with baseline ratings (paired t test; $P < 0.001$). Importantly, there was also a significant reduction of fear as measured from session 1 to session 6, which was assessed 2 days after the last cortisol treatment (paired t test; $P = 0.001$). No significant difference in fear ratings was observed between sessions 5 and 6 (paired t test; $P > 0.6$). Together, these findings indicate that cortisol administration reduced stimulus-induced fear and that this treatment effect was maintained when subjects were investigated again 2 days after the last cortisol administration. Cortisol administration also significantly reduced stimulus-induced avoidance as compared with placebo treatment (repeated-measures ANOVA, $F = 6.54$; $df = 1, 17$; $P = 0.02$), which presumably resulted from reduced stimulus-induced fear. For subjective physical reactions, there was no significant treatment effect (repeated-measures ANOVA, $F = 1.91$; $df = 1, 17$; $P = 0.2$). Cortisol treatment in spider phobia did not induce a phobia-unrelated anxiolytic effect, as measured with the State-Trait Anxiety Inventory questionnaire (repeated-measures ANOVA, $F = 0.04$; $df = 1, 17$; $P = 0.9$).

Discussion

The findings of these two studies indicate that glucocorticoid administration reduced phobic fear in both types of phobias examined. In social phobia, the acute administration of cortisone (which is rapidly metabolized into the endogenous glucocorticoid cortisol) reduced subjective fear during the anticipation, exposure, and recovery phase of the stressor. After cortisone administration, heart-rate reactivity was reduced during the

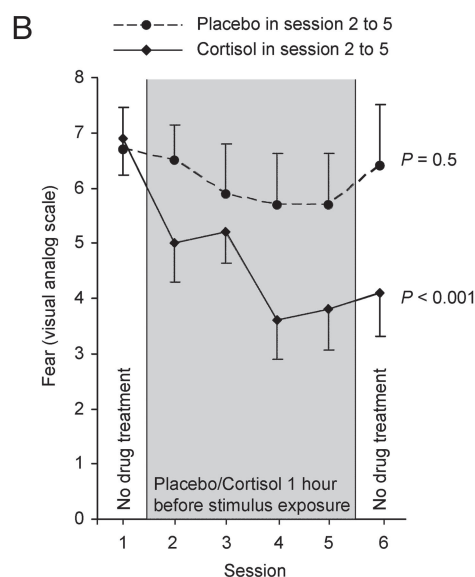


Fig. 3. Spider phobia. (A) The phobic stimulus consisted of a color photograph of a spider. (B) Effect of cortisol on stimulus-induced fear in spider phobia. Fear symptoms were assessed by using a visual analog scale ranging from 0 (no fear) to 10 (maximal fear). On sessions 2–5, subjects were administered either cortisol (10 mg) or placebo 1 h before exposure to the phobic stimulus, whereas no pharmacological treatment was given on sessions 1 and 6. Fear ratings are depicted as mean \pm SEM. P values indicate significance of symptom change across sessions for each treatment group.

anticipation phase of the TSST and returned faster to the baseline after the TSST. We further found that stress-induced cortisol release in placebo-treated social phobics correlated negatively with fear ratings, suggesting that endogenously released cortisol in the context of a phobic situation may buffer fear symptoms. Maximal endogenous cortisol levels were comparable with those induced by cortisone administration. Before the TSST or in social phobics who were not exposed to the TSST, cortisone only induced a trend toward less fear. It is important to mention that even without an experimental stressor, socially phobic subjects had a certain level of phobic fear, likely resulting from inevitable social interactions with the investigator. Therefore, one would expect cortisone also to reduce social fear under this “control” condition. However, as fear levels were low, a floor effect may have prevented this reduction from becoming significant. Very similar to the findings in social phobia, pharmacologically elevated cortisol levels reduced phobic fear in subjects with spider phobia. In particular, our findings indicate that repeated administration of cortisol led to a progressive

reduction of stimulus-induced fear that was maintained beyond the treatment period.

Although the two types of phobias differ with regard to the phobic stimulus and specificity of the stimulus (2), both phobias are characterized by vivid and excessive stimulus-associated fear memory. In this study, we were particularly interested in exploring the possibility whether our previous findings indicating that glucocorticoids impair retrieval of emotionally arousing information may apply to fear memory in phobia as well. Extensive evidence from studies in amnesic patients, human imaging studies, and lesion studies in animals indicates that the medial temporal lobe (MTL) is crucially involved in memory retrieval and that activation of the MTL is associated with successful memory retrieval (23–25). In support of the view that memory retrieval is important in phobias, a functional MRI study showed that the MTL in patients with spider phobia becomes activated by viewing a film about spiders, but that after successful completion of cognitive-behavioral therapy, the MTL is no longer activated (26). Furthermore, a positron-emission tomography (PET) study in patients with social phobia reported that after successful psycho- or pharmacotherapy, the MTL gets less activated by public speaking (27). Using PET imaging in healthy humans, we previously found that acutely administered cortisone reduced blood flow in the MTL during memory retrieval, an effect that correlated with the degree of memory retrieval impairment (14). Furthermore, systemic administration of glucocorticoids to rats shortly before retention testing induced memory retrieval impairments of contextual memory (17), a task that depends on the MTL (23), whereas local infusions of a glucocorticoid receptor agonist into the hippocampus induced memory retrieval impairments comparable with those seen after systemic administration (16). Together, these findings suggest that in the present studies, elevated cortisol levels may have reduced stimulus-induced fear by inhibiting MTL activity during memory retrieval.

Because phobia-related retrieval processes cannot be measured directly, it cannot be ruled out that cortisol, perhaps in addition to influencing memory retrieval, may have reduced fear by exerting a direct anxiolytic effect or by modulating other systems involved in the expression of fear. However, in favor of the view that glucocorticoids had reduced fear by inhibiting the retrieval of aversive memories, we recently found that cortisol administration to patients with posttraumatic stress disorder, another chronic anxiety disorder, reduced reexperiencing of the trauma, a direct measure of memory retrieval (21). In addition, in the present study, glucocorticoid administration did not affect phobia-unrelated anxiety, mood, wakefulness, or calmness, suggesting that this hormone reduced phobic fear specifically. Moreover, recent findings indicating that acute cortisol elevations cause heightened arousal ratings of neutral stimuli (28) make a general or direct anxiolytic effect of glucocorticoids unlikely.

The findings of the present studies may have several important implications. The results provide insight into the behavioral consequences of a stress-induced release of glucocorticoids. Our findings indicating that elevated glucocorticoid levels in the context of a fearful situation turn down fear symptoms in phobic subjects suggest that cortisol release may represent an adaptive response. This notion is in line with the broader view that glucocorticoid release during acute stress represents an adaptive response that helps the organism to deal with a wide spectrum of internal and external demands (29–31). The present findings may also have important clinical implications. Because current psycho- and pharmacotherapeutic treatment options for phobias are not satisfactory (32, 33), the development of efficacious fear-reducing treatments is needed. Our findings in two distinct types of phobias indicate that the administration of low-dose glucocorticoids reduced phobic fear. Furthermore, and consis-

tent with findings of animal experiments (34, 35), repeated administration of glucocorticoids induced a progressive reduction of fear ratings and, thus, might have facilitated the extinction of phobic fear. Although we did not further examine this issue here, such a putative extinction effect may have resulted from the inhibitory effect of cortisol on the retrieval of fear memory, as subjects learn that the phobic stimulus becomes less fearful under elevated glucocorticoid levels. In addition to the inhibitory effect on memory retrieval, elevated glucocorticoid levels are known to enhance the long-term consolidation of new information (36–38). It is therefore possible that glucocorticoids may have further promoted fear extinction by facilitating the storage of corrective experiences, as evidenced by recent findings indicating that glucocorticoids enhance the consolidation of fear extinction memory (39, 40). Thus, glucocorticoid treatment, in combination with exposure techniques in cognitive-behavioral therapy, may help to reduce fear and promote extinction of phobic fear. In addition to these potentially beneficial effects in phobia, glucocorticoids also reduce retrieval of traumatic memory (21). Therefore, by a common mechanism of reducing memory retrieval, glucocorticoids may be suited for the treatment of phobias and posttraumatic stress disorder.

Methods

Social Phobia Study. Subjects. For the social stress experiment, 30 male patients who fulfilled the criteria for social phobia were recruited via advertisement. For the experiment under resting conditions, 19 additional male patients were investigated. Diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (2). Patients were excluded from the study if they met any of the following conditions: a recent history of systemic or oral glucocorticoid therapy, axis I disorder other than social phobia, personality disorders other than insecure, dependent, or compulsive personality disorder (diagnosed with structured clinical interview for DSM-IV) (41), smoking >15 cigarettes per day, neurological or physical problems, pharmacological treatment, or behavioral therapy. After describing the study to the patients, written informed consent was obtained. The study was approved by the ethics committee of the University of Zürich. Patients who remained eligible at the end of the diagnostic phase were randomly assigned to a double-blind, placebo-controlled design. Nine subjects were excluded from the study because of concomitant medication or ineffective elevation of cortisol levels by the cortisone administration. All subjects received 150 Swiss francs and were offered the possibility to attend a cognitive-behavioral group therapy after the experiment.

Procedure and measurements. The experiments took place in the laboratories of the Department of Clinical Psychology and Psychotherapy and the Division of Psychiatry Research of the University of Zürich between 1400 and 1700 hours. The social stress experiment consisted of three consecutive phases after the oral administration of cortisone (25 mg; Novartis Pharma, Basel, Switzerland) or placebo (Fig. 1A): (i) an initial 60-min resting period to allow absorption of medication, (ii) a socio-evaluative stress test (30 min), and (iii) a final 60-min recovery and debriefing period. After absorption, cortisone is quickly metabolized into hydrocortisone (cortisol), which readily enters the brain (29). TSST enables a naturalistic exposure to a socio-evaluative stressful situation (42) and consists of a speech task and a mental arithmetic task, performed in front of an audience and a video camera (22). Briefly, the stress test started with a written instruction informing the subjects that they have 10 min to prepare themselves for a speech task in which they are required to explain within 5 min why someone should hire them. The speech task was followed by an unprepared 5-min mental arithmetic task. Before substance administration, the subjects were connected to a heart-rate monitor (Polar S810; Polar

Electro Oy, Kempele, Finland) and the collection of saliva by using the Salivette (Sarstedt, Rommelsdorf, Germany) was demonstrated, followed by the first sample collection. Four additional saliva samples were collected (60, 70, 100, and 145 min after substance administration). The saliva samples were stored at -20°C until required for biochemical analysis. Fear- and mood-related symptoms were assessed repeatedly before and after the stress exposure (Fig. 1A). Subjects rated their subjective actual discomfort in the dimensions anxiety, physical reaction, and avoidance seven times during the procedure by using visual analog scales ranging from 0 (no symptoms) to 10 (maximal symptoms). Furthermore, state anxiety was measured by using the German version (43) of the Spielberger State-Trait Anxiety Inventory (44). This questionnaire measures acute subjective anxiety at the moment of assessment. Lastly, the mood/activity questionnaire (Mehrdimensionaler Befindlichkeitsfragebogen) was used, which consists of three scales termed elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness (45). For the experiment under resting conditions, fear and mood were assessed and saliva was sampled at the same time points as in the social stress experiment (Fig. 1A), but subjects were not exposed to social stress and, instead, were told to rest quietly and were allowed to read magazines.

Hormone analyses. Free cortisol in saliva was analyzed by using a commercially available immunoassay (CLIA; IBL-Hamburg, Hamburg, Germany). The inter- and intraassay coefficients of variation were $<10\%$. To reduce error variance caused by imprecision of the intraassay, all samples of one subject were analyzed in the same run.

Statistics. Group differences in demographic and clinical characteristics and baseline values (before substance administration) were analyzed with unpaired t tests. Effects of cortisone administration on salivary cortisol concentrations, fear symptoms, heart rate, and mood were analyzed with two-way repeated-measures ANOVAs with treatment as a between-subject factor and time points as a within-subject factor. Univariate ANOVAs were used to analyze treatment effects at a certain time point. The measurement before substance administration was included as a covariate in the ANOVAs to control for subtle treatment-independent group differences. The areas under the curve were calculated with the trapezoid formula (46), aggregating the seven measurements of the visual analog scales anxiety, physical reaction, and avoidance. All tests were two-tailed and a P value of <0.05 was considered statistically significant. All variables were normally distributed (Kolmogorov–Smirnov test: $P > 0.1$ for all variables).

Spider Phobia Study. Subjects. Male and female subjects with spider phobia were recruited via newspaper advertising. Twenty subjects (4 males and 16 females) who fulfilled ICD-10 criteria for specific phobia for spiders were included in the study. Exclusion criteria included acute or chronic medical conditions, a recent history of systemic or oral glucocorticoid therapy, psychiatric problems other than specific phobia for spiders, and psychotropic drug treatment. German versions (47) of the Spider Phobia Questionnaire (48) and

the Fear of Spider Questionnaire (49) were used to assess fear of spiders. After complete description of the study to the subjects, written informed consent was obtained. Subjects received 100 Swiss francs for participation. The study was approved by the ethics committee of the University of Zürich.

Procedure and measurements. Patients were exposed to a phobic stimulus on six sessions distributed over 2 weeks (each week on Monday, Wednesday, and Friday). Each session took place between 1700 and 1900 hours. Patients were randomly assigned to receive either an oral administration of cortisol (10 mg of hydrocortisone; Galepharm, Küssnacht, Switzerland) or placebo 1 h before the presentation of the stimulus on sessions 2–5. On sessions 1 and 6, there was no drug treatment before stimulus presentation to assess baseline symptoms and to examine whether fear ratings return to baseline after cessation of the treatment, respectively. To keep the possibility of negative side effects with repeated administrations of glucocorticoids as low as possible, we selected a low-dose treatment regimen (10 mg of cortisol), as used in our posttraumatic stress disorder study (21). The phobic stimulus consisted of a color photograph of a spider and was presented for 4 s (Fig. 3A). Subjects were asked to look at the photograph during the entire presentation time and, immediately after presentation, to rate their perceived fear, desire to look away from the picture (avoidance), and subjective physical reactions (e.g., sweating or trembling) induced by the picture on visual analog scales. Additionally, we assessed general anxiety levels on each session by using the State-Trait Anxiety Inventory (44). Saliva samples were taken immediately before picture presentation on sessions 1 and 6. On sessions 2–5, samples were taken both before and 1 h after pharmacological treatment. Cortisol analysis was performed as described above.

Statistics. Group differences in demographic and clinical characteristics and in cortisol concentrations were analyzed with unpaired t tests. Cortisol treatment effects on fear symptoms were analyzed with two-way repeated-measures ANOVAs with treatment as a between-subject factor and session as a within-subject factor. The measurement before substance administration (day 1) was included as a covariate in the two-way repeated-measures ANOVAs. Changes in symptom ratings over the sessions within a treatment group were analyzed with one-way repeated-measures ANOVAs. Intersession differences within a group were analyzed with paired t tests. All tests were two-tailed, and a P value of <0.05 was considered statistically significant. All reported results were corrected by using the Greenhouse–Geisser procedure, where appropriate. All variables were normally distributed (Kolmogorov–Smirnov test: $P > 0.1$ for all variables).

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