Glucocorticoids enhance extinction-based psychotherapy

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Behavioral exposure therapy of anxiety disorders is believed to rely on fear extinction. Because preclinical studies have shown that glucocorticoids can promote extinction processes, we aimed at investigating whether the administration of these hormones might be useful in enhancing exposure therapy. In a randomized, double-blind, placebo-controlled study, 40 patients with specific phobia for heights were treated with three sessions of exposure therapy using virtual reality exposure to heights. Cortisol (20 mg) or placebo was administered orally 1 h before each of the treatment sessions. Subjects returned for a posttreatment assessment 3–5 d after the last treatment session and for a follow-up assessment after 1 mo. Adding cortisol to exposure therapy resulted in a significantly greater reduction in fear of heights as measured with the acrophobia questionnaire (AQ) both at posttreatment and at follow-up, compared with placebo. Furthermore, subjects receiving cortisol showed a significantly greater reduction in acute anxiety during virtual exposure to a phobic situation at posttreatment and a significantly smaller exposure-induced increase in skin conductance level at follow-up. The present findings indicate that the administration of cortisol can enhance extinction-based psychotherapy.

Results

The cortisol group and the placebo group consisted each of 20 patients (11 males, 9 females). The groups did not differ significantly in demographic and clinical characteristics, or in any of the baseline measurements taken before treatment (Table 1). On all sessions with pharmacological treatment (i.e., treatment sessions 1–3), subjects who had received cortisol had significantly higher salivary cortisol concentrations before (P ≤ 0.001) and after (P ≤ 0.007) VR exposure than subjects who had received placebo (Table S1). No differences in baseline salivary cortisol concentrations were found between the treatment groups on any of the study days (P ≥ 0.332). None of the patients reported adverse effects due to substance administration.

Effects of VR Exposure. We found a significant reduction of fear as measured with the acrophobia questionnaire (AQ) from pretreatment assessment (59.3 ± 2.8; mean ± SE) to posttreatment assessment (35.7 ± 2.6; F1,35 = 18.135; P < 0.001), and follow-up (30.1 ± 2.8; F1,35 = 18.636; P < 0.001). The controlled effect size from pretreatment to posttreatment assessment was d = 1.3 and from pretreatment to follow-up d = 1.6. Also in the danger expectancy scale (DES) fear symptoms decreased from pretreatment (18.1 ± 0.6) to posttreatment (14.8 ± 0.7; F1,34 = 17.828; P < 0.001) and follow-up (12.8 ± 0.6; F1,35 = 15.926; P < 0.001). No significant


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symptom decrease was observed with the anxiety expectancy scale (AES) and with the attitude toward heights questionnaire (ATHQ). No significant symptom change was measured from posttreatment to follow-up in any of the questionnaires (AQ, DES, ATHQ, and AES) (Table 1). Performance in the behavioral avoidance test (BAT) was enhanced from pretreatment (4.1 ± 24.2) to posttreatment (5.9 ± 3.5; placebo, 5.2 ± 3.5; $F_{1,34} = 5.090; P < 0.031$) (Fig. 1). The controlled effect size for cortisol at posttreatment was $d = 0.6$ and at follow-up $d = 0.6$. Sex did not influence the cortisol effect (interaction sex X drug, $P > 0.4$). There was a significant difference for the AES at follow-up (cortisol, 11.5 ± 0.8; placebo, 14.2 ± 0.8; $F_{1,34} = 5.322; P = 0.027$). The controlled effect size for cortisol at follow-up was $d = 0.6$. Sex did not influence the cortisol effect on AES (interaction sex X drug, $P > 0.2$). We found a trend difference for the AES at follow-up (cortisol, 24.7 ± 1.4; placebo, 28.4 ± 1.4; $F_{1,34} = 3.512; P = 0.07$) and no significant difference for the ATHQ. There was a trend toward better performance of the cortisol group compared with the placebo group in the BAT at follow-up (cortisol, 5.9 ± 0.2; placebo, 5.2 ± 0.2; $F_{1,34} = 3.767; P = 0.061$) but not at posttreatment (cortisol, 5.8 ± 0.2; placebo, 5.2 ± 0.2; $F_{1,34} = 2.435; P = 0.128$). The BAT scale ranges from 0 to 6, where 0 means least fear. Compared with the placebo group, the cortisol group showed significantly lower anxiety (as measured in subjective units of discomfort (SUDs)) while going up with the elevator during VR exposure (difference score SCL, in microsiemens) in the cortisol group compared with the placebo group (cortisol, 0.073 ± 0.093; placebo, 0.393 ± 0.106; $F_{1,19} = 5.024; P = 0.042$) (Fig. 2). Sex did not significantly influence the cortisol effect (interaction sex X drug, $P > 0.2$). The analysis at posttreatment showed a trend toward a smaller SCL difference score in the cortisol group (cortisol, 0.235 ± 0.091; placebo, 0.475 ± 0.106; $F_{1,19} = 2.906; P = 0.105$). SCL during the 60-s period on the floor did not differ significantly between treatment groups at posttreatment and follow-up ($P > 0.185$; Tables S2 and S3 show SCL data during the 60-s periods on the floor and roof).

**Skin conductance.** Due to technical reasons, skin conductance level (SCL) was only available from 25 subjects at posttreatment and from 20 subjects at follow-up. The treatment groups did not differ significantly in demographic and clinical characteristics or in any of the baseline measurements taken before treatment (Tables S2 and S3). Due to the smaller sample sizes, we analyzed the data for possible outliers and found that all values lay within 2.3 times the SD from the mean (data were normally distributed; Kolmogorov–Smirnov test, $P > 0.36$). At follow-up, there was a significantly smaller SCL increase from the 60-s period on the floor to the 60-s period on the roof after going up with the elevator during VR (difference score SCL, in microsiemens; $P = 0.031$) (Fig. 2). Sex did not significantly influence the cortisol effect (interaction sex X drug, $P > 0.2$). The analysis at posttreatment showed a trend toward a smaller SCL difference score in the cortisol group (cortisol, 0.235 ± 0.091; placebo, 0.475 ± 0.106; $F_{1,19} = 2.906; P = 0.105$). SCL during the 60-s period on the floor did not differ significantly between treatment groups at posttreatment and follow-up ($P > 0.185$; Tables S4 and S5 show SCL data during the 60-s periods on the floor and roof).

**Discussion**

The results of the present study indicate that cortisol facilitates the effects of VR exposure therapy. As measured with the acrophobia questionnaire, a standard questionnaire to reliably assess fear of heights (37), patients who received cortisol together with the three VR exposure sessions, showed significantly greater reductions in phobic fear both at posttreatment and at 1-mo follow-up (Fig. 1), compared with patients who received placebo. The controlled (for placebo treatment) effect size of the cortisol treatment was $d = 0.6$ at follow-up, which corresponds to a medium effect size. Acute anxiety as measured in SUDs while going up with the elevator during VR exposure was significantly more reduced in patients receiving cortisol than in patients receiving placebo at posttreatment, but not at follow-up. In the BAT, which consists of a real-life heights situation, there was only little room for drug-related improvements, as the mean score in the placebo group was 5.2 at follow-up (maximal score 6). In the cortisol group the mean score

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**Table 1. Demographic and clinical characteristics and baseline measurements at pretreatment assessment**

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Cortisol group</th>
<th>Significance, $P$</th>
</tr>
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<tr>
<td>Females/males</td>
<td>9/11</td>
<td>9/11</td>
<td>1.0</td>
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<tr>
<td>Age (yr)</td>
<td>40.2 (2.6)</td>
<td>42.8 (2.4)</td>
<td>0.461</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (1.1)</td>
<td>25.6 (0.8)</td>
<td>0.558</td>
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<tr>
<td>Severity primary diagnosis</td>
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<td>5.4 (0.2)</td>
<td>0.874</td>
</tr>
<tr>
<td>BDI total score</td>
<td>5.7 (1.2)</td>
<td>4.0 (1.0)</td>
<td>0.280</td>
</tr>
<tr>
<td>ASI total score</td>
<td>17.9 (1.8)</td>
<td>16.2 (1.8)</td>
<td>0.498</td>
</tr>
<tr>
<td>STAI trait total score</td>
<td>39.2 (1.8)</td>
<td>36.1 (1.4)</td>
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</tr>
<tr>
<td>ITQ</td>
<td>5.3 (1.2)</td>
<td>4.2 (1.2)</td>
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<td>AQ</td>
<td>58.9 (4.4)</td>
<td>58.4 (4.1)</td>
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</tr>
<tr>
<td>ATHQ</td>
<td>41.5 (2.7)</td>
<td>39.3 (2.0)</td>
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</tr>
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<td>DES</td>
<td>18.3 (1.0)</td>
<td>18.6 (0.9)</td>
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<td>AES</td>
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<td>Treatment credibility</td>
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<td>22.8 (0.6)</td>
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<td>SUD</td>
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<td>BAT score</td>
<td>4.3 (0.4)</td>
<td>4.1 (0.4)</td>
<td>0.792</td>
</tr>
</tbody>
</table>

Data presented as mean (SEM). AES, anxiety expectancy scale; AQ, acrophobia questionnaire; ASI, anxiety sensitivity index; ATHQ, attitude toward heights questionnaire; BDI, behavioral avoidance test; BMI, body mass index; DES, danger expectancy scale; ITQ, immersive tendencies questionnaire; STAI, state-trait anxiety inventory; SUD, subjective units of discomfort.
at follow-up was 5.9, resulting in a trend in treatment effect. Further studies are needed to investigate the cortisol effects in more challenging real-life situations and using reinstatement and renewal tests. Finally, we found evidence that cortisol reduced VR.

Materials and Methods

Subjects. Subjects aged 18–60 with fear of heights (acrophobia) were recruited via newspaper advertisements and flyers posted at the University of Basel and health institutions. A total of 260 subjects responded and, after a telephone screening, 75 subjects were invited for a diagnostic assessment with the diagnostic interview for mental disorders (DIPS) (50). A total of 42 patients (23 males and 19 females) who fulfilled criteria for specific phobia environmental-type based on the DSM-IV (51) were included in the study. Exclusion criteria were: a recent history of systemic or oral glucocorticoid therapy, another axis I disorder that was considered to be more impairing and distressing than the acrophobia, severe acute or chronic disease, pregnancy and lactation, current pharmacological treatment, or behavioral therapy. Pregnancy was determined by means of a urine pregnancy test that was performed for all female patients before administration of study medication. Two participants were excluded after allocation to study groups. One participant refrained from study participation between treatment sessions 1 and 2; another participant was excluded because of dizziness during VR therapy. Both subjects were allocated to the cortisol group. The remaining 40 patients completed the study and entered the analyses.

Procedure and Measurements. Treatment. The study took place at the laboratories of the Department of Clinical Psychology and Psychotherapy of the University of Basel. Participation included six appointments: an initial screening session to clarify study eligibility and to assess symptoms before treatment (pretreatment assessment), three treatment sessions (treatment sessions 1–3) within 1 week (Monday, Wednesday, and Friday), an assessment 3–5 d after the last treatment session (posttreatment assessment), and a follow-up assessment 28–35 d after the last treatment session (follow-up assessment). During each treatment session, either cortisol (20 mg, 2 tablets of hydrocortisone; Galepharm, Küsnacht, Switzerland) or placebo (2 similarly looking tablets) was administered 1 h before each of the three VR sessions. The initial 1-h resting period allowed the absorption of the medication before starting the VR session. On the pretreatment assessment, posttreatment assessment, and on the follow-up assessment, no medication was administered. During these assessments, participants had limited and structured exposure to the VR heights environment (using an elevator in the same VR environment as used for the treatment sessions) during a behavioral test in VR. During this behavioral test, participants were asked about their fear while going up with the elevator by means of SDSs on a scale ranging from 0 to 100 (100 being the most intense fear). To prepare the patients for the exposure session, the patients received some psychoeducative material about exposure therapy and instructions on how to cope with former avoidance strategies during pretreatment assessment. No other cognitive-behavioral techniques, such as breathing or relaxation techniques, were used. VR treatment. The exposure treatment took place in a temperature-controlled environment (temperature was between 19.7 °C and 27 °C, mean 22.3 °C) and sound attenuated experimental room (temperature was between 19.7 °C and 27 °C, mean 22.3 °C) and sound-attenuated experimental room (temperature was between 19.7 °C and 27 °C, mean 22.3 °C) and sound-attenuated experimental room (temperature was between 19.7 °C and 27 °C, mean 22.3 °C) and sound-attenuated experimental room (temperature was between 19.7 °C and 27 °C, mean 22.3 °C). During the exposure session the room was darkened. The participant stood on a wooden platform (1.5 x 2.1 feet high; height above floor about 6 inches). Before the exposure session started, physiological sensors and a headset with...
integrated video display glasses (head-mounted display) and headphones were attached. Via these glasses, patients were exposed to a VR height environment (Virtual Reality Medical Center, San Diego, CA) that was simulated by a computer program. A sensor registered head movements and altered the display to reproduce a change in gaze direction.

The therapist controlled the treatment via a personal computer keyboard located in the control room and adapted the standardized therapy protocol depending on the strength of reported fear of the patient. The subjects were instructed to move their heads and look around. Patients were guided through a VR height environment with different platforms connected by bridges and elevators. All patients were systematically guided through the environment and had to pass different predefined stations with increasing difficulty. Patients started the treatment session with using a lift at a rather low building and finished it with crossing a long and small bridge connecting two very high platforms. The following predefined schema for the treatment session in VR was used: patients had to stay at a particular station for at least 60 s. During this period they had to give two SUDs, the first one after 30 s and the second one after another 30 s. The second SUD at a particular station was used as “reference anxiety” for how long a patient had to stay at a particular station. If the second SUD was 30 or below, the patient was guided to the next predefined station. If the second SUD was above 30, the patient had to stay at this station until the anxiety had decreased at least 20%. After a decrease of at least 20%, the therapist asked for another further SUD. If anxiety did not further decrease, the patient was guided to the next station. Patients had to stay at this station until no further decrease occurred or until seven SUDs were taken, which was predefined as a maximum for each station. SUDs were asked every 30 s, therefore a patient never stayed longer than 210 s at a station. This procedure was applied at each station. A maximum of 10 stations was available. Every patient stayed for 20 min in the VR. The time spent at each station and the number of stations varied between patients and between sessions.

Participants were instructed to avoid cognitive avoidance strategies and the cognitive avoidance was measured with several questions afterward.

Self-Report Measures. Fear of heights questionnaires. The following measures were applied at pretreatment, posttreatment, and for the follow-up assessments to measure fear of heights: (i) The German translation of the anxiety subscale of the AQ (37). This questionnaire describes 20 situations that can cause fear of heights (e.g., crossing a bridge, walking on a roof after going up with the elevator). Patients evaluate their attitudes toward heights by answering questions on a 7-point scale from 0 = “no anxiety at all” to 6 = “very anxious” (range 0–6). (ii) The ATHQ, German version (53) and (iii) the DES, German version (54) to assess dysfunctional cognitions. The ATHQ consists of six questions assessing participants’ attitudes toward height situations (e.g., “I think heights are...good/ bad, secure/insecure”). Patients evaluate their attitudes toward heights by 12 adjectives on an 11-point scale ranging from a positive (0) to a negative (10) adjective (range 0–60; α = 0.81). The DES consists of five items. Participants rate the likelihood that each of the listed harmful events (e.g., “you might slip and fall over the guard rail on the observation deck”) will pass through their minds while being in a height situation on five-point scales (not likely at all (1), probably not (2), maybe (3), quite likely (4), or definitely (5), range 5–25) (4). The AES, German version (55) to assess anxiety symptoms in a height situation. The AES consists of 10 items describing anxiety symptoms (e.g., “you could feel dizzy”). Participants rate the likelihood of experiencing these symptoms while being in a height situation on the same five-point scale as described above (range 10–50).

Acute fear in height situations. During the behavioral test in VR, participants rated their anxiety while going up with the elevator by means of verbal SUDs on a 10-point scale from 0 = “no anxiety at all” to 10 = “extremely anxious” (range 0–10). The first SUD was taken after the completion of the pretest, posttreatment, at the different pretest, posttreatment, and during the follow-up assessment, participants performed a BAT consisting of a real-life heights situation (going up an outdoor staircase with three levels). During the BAT, the performance was rated on a scale from 0 to 6. One point was given for each completed level and another point for looking down for 30 s at each level.

Trait anxiety and depression. Anxiety and depressive symptoms were assessed with the German versions of the state-trait anxiety inventory (STAI, German version) (56), the anxiety sensitivity index (ASI, German version) (57), and the Beck depression inventory (BDI, German version) (58).

Presence. At pretreatment assessment, participants answered five questions taken from the immersive tendencies questionnaire (ITQ), which measures, by means of ratings on a 7-point scale based on the semantic differential principle, differences in disposition to experience presence. Like the semantic differential, each ITQ item is anchored at the ends by opposing descriptors. Unlike the semantic differential the ITQ scale includes a midpoint anchor (52).

Treatment credibility. Treatment credibility/expectancy (score ranging from 0 to 30) were completed by all of the participants after the psychoeducational part at pretreatment assessment and the first and last exposure session (59). Participants were asked at each exposure session and at posttreatment and follow-up on a scale from 5 to 3 (placebo to cortisol) to indicate whether they believed they were assigned to active medication or placebo. We did not systematically obtain reports of adverse effects although the subjects were routinely asked at the beginning and end of each session if they were experiencing any difficulties.

Skin Conductance Level. Electrodermal activity was measured using 11-mm Ag/AgCl electrodes filled with isotonic electrode paste (60) attached to the volar surfaces of the medial index and middle fingers (with a constant 0.5 V passed between the electrodes). Body movement was assessed using an accelerometer attached to the right shoulder to allow identification of movement artifacts. All physiological channels were sampled continuously at a rate of 1,000 Hz using a BIOPAC MP150 amplifier and Acqknowledge software (Biopac System Inc). Electrodermal activity was edited for artifacts and 1-Hz lowpass filtered to extract the mean value for each station. SUDs were applied at the raw signals for artifacts and extract physiologically meaningful parameters: The raw signal of electrophysiological activity was edited for artifacts and 1-Hz lowpass filtered to extract the average SCL during the phases of the experiment. Mean values were calculated for four time segments during the behavioral test in VR (60-s period immediately before the VR exposure, 1-Hz lowpass filter, 60 s after the VR exposure upward), and 60 s after the VR exposure downward). Additionally, a difference score was built by subtracting the mean value of a physiological variable during the 60-s period on the floor from the mean value of a physiological variable during the 60-s period on the roof after going up with the elevator.

Statistics. Data were entered into the SPSS statistics package for Macintosh (SPSS, 17.0) by research assistants blind to condition. Group differences in demographic and clinical characteristics and cortisol levels at baseline, before and after VR exposure, were analyzed with unpaired t tests or X2 tests.

VR exposure effects. To analyze VR-induced symptom change from pre- to posttreatment to posttreatment and follow-up, variables of interest (AQ, DES, AES, ATHQ, BAT, and SUD) were analyzed with repeated-measures ANCOVAs with symptoms at certain time points as within-subject factors, age as covariate, and sex and condition as between-subject factors. The calculated effect size (Cohen’s d) was calculated for significant variables via the formula: (meanpretreatment+follow-up − meanpretreatment)/(SDpretreatment+follow-up + SDpretreatment+follow-up)/2 (61, 62).

Drug-dependent analyses: Pretreatment, posttreatment, and follow-up. To compare the outcome of the two treatment conditions (exposure + placebo vs. exposure + cortisol), we used univariate ANCOVAs with treatment condition as between-subject factor, posttreatment, and follow-up measures as dependent variables (AQ, DES, AES, BAT, and SUD) and corresponding pre- to posttreatment baseline measures as covariate (63, 64). Furthermore, we included age as covariate and sex as cofactor. The controlled effect size (Cohen’s d) was calculated for significant variables via the formula: (meanexposure+cortisol − meanexposure+placebo)/(SDexposure+cortisol + SDexposure+placebo)/2 (61, 62).

Skin conductance level. Due to technical failure, not all physiological measurements could be used, resulting in a subject sample of 25 for posttreatment (11, placebo group; 14, cortisol group) and 20 at follow-up (9, placebo group; 11, cortisol group). We conducted ANCOVAs with treatment condition as between-subject factor, posttreatment, and follow-up physiological measures (i.e., difference score SCL) as dependent variable and the corresponding pretreatment baseline measure as covariate. Furthermore, we included age as covariate and sex as cofactor.

Because age and sex have been shown to influence glucocorticoid effects on memory and emotional processes (65–68), we included a priori age as covariate and sex as cofactor in the behavioral and SCL analyses. All tests were two-tailed and a P value < 0.05 was considered statistically significant.
All variables were normally distributed (Kolmogorov–Smirnov test: P > 0.1 for all variables). All reported results were corrected by using the Greenhouse–Geisser procedure, where appropriate.

20. Beck Depressionsinventar (BDI) (Huber, Bern).

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