



Stress hormones during flooding therapy and their relationship to therapy outcome in patients with panic disorder and agoraphobia

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ABSTRACT

In spite of excessive fear during a panic attack, studies have found no or little evidence for an activation of cortisol during natural panic attacks. Whether this phenomenon is related to psychopathology or outcome of psychotherapy is unknown. In this study, 10 patients with panic disorder and agoraphobia were treated with cognitive behavioural therapy including 3 in-vivo exposures (flooding) to individual phobic situations. Before, during and after exposure, the level of subjective fear was assessed and blood was collected simultaneously. Cortisol and ACTH were analysed from plasma. Ten matched healthy control subjects went through the same procedure. Fear and stress hormones during exposure were compared in patients and controls as well as related to therapy outcome at the end of therapy and 2 follow-ups in patients. Results showed that the concentrations of cortisol and ACTH did not significantly increase during exposure. Patients' cortisol concentrations were higher than those of controls at baseline and during exposure, while ACTH concentrations were comparable before and during exposure, and even lower than those of controls at recovery. Cortisol concentrations were moderately but consistently correlated to therapy outcome, i.e. patients with least cortisol release during exposure profited least from therapy. The study showed that a lack of stimulation of the HPA system at repeated confrontation with the phobic situation was related to therapeutic outcome. Mechanisms of action via the influence of cortisol on extinction learning or the inhibition of central excitatory neurotransmission are conceivable.

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1. Objectives of the study

During panic attacks, patients with panic disorder experience excessive fear accompanied by a range of seemingly dangerous body sensations like tachycardia, dyspnoea, trembling, sweating, chest pain, dizziness, paresthesia in the extremities and visual dysfunction. Accordingly, they experience massive stress, often with fear of losing control or even fear of death. Therefore, one would expect a strong activation of the hypothalamus-pituitary-adrenal (HPA) axis in those patients. Astonishingly, studies that have measured cortisol during natural panic attacks so far found either no (Woods et al., 1987; Cameron et al., 1987) or little (Bandelow et al., 2000) increase of this stress hormone in patients with panic disorder.

The occurrence of panic attacks in certain situations, their association with the context and its subsequent generalization is commonly assumed to be the basis of panic disorder and

agoraphobia due to classical and instrumental fear conditioning (Mowrer, 1939). Similarly, exposure therapy is regarded as the clinical equivalent to extinction training (Bouton et al., 2001; Mineka and Zinbarg, 1996). As such, the investigation of HPA axis function during situationally induced panic attacks in panic disorder is still of considerable interest with respect to the known role of stress hormones in fear conditioning, retrieval, reconsolidation and fear extinction (for review see McGaugh and Roozendaal, 2009, 2002; Myers and Davis, 2007).

So far, consequences of the observed lack of HPA responsiveness in patients with panic disorder and agoraphobia during in-vivo exposures have not been investigated in a prospective manner. Further, ACTH has not been monitored in real-life panic attacks so far, although both stress hormones are often dissociated in their response pattern (Bornstein et al., 2008). For this reason, we closely monitored cortisol and ACTH concentrations during in-vivo exposure therapy in 10 patients with agoraphobia and panic disorder and compared them to matched healthy controls which underwent the same procedure. We further analysed whether fear levels or stress hormone concentrations during exposure can predict therapy outcome in the patients.

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2. Methods and materials

2.1. Participants

Ten outpatients (six women) with panic disorder and agoraphobia from our clinic received cognitive behavioural therapy. Blood was obtained during exposures (in one patient blood collection failed during the 3rd exposure). Ten healthy age- (± 2 years) and sex-matched control subjects without phobic or other mental disorder participated in the study. Psychiatric diagnoses or mental health respectively, were determined by a semi-structured interview according to DSM – IV criteria (Sheehan et al., 1998; German Version 5.0.0) and the severity of the anxiety disorder ranked by usage of the clinical global impression (CGI). Somatic health was assessed by physical examination, ECG and a range of laboratory tests including a drug screening. Exclusion criteria were severe other mental disorders, severe somatic illness constraining fitness for exposure therapy, pregnancy or lactation or a disrupted sleep-wake pattern. Patients either had four weeks wash-out phase for psychopharmacological treatment before the beginning of the study or were stable on psychopharmacological medication for at least eight weeks (three patients were on fluoxetine, venlafaxine or escitalopram). Groups did not differ in age (patients: mean age 36.9 ± 9.7 years; control subjects: mean age 37.3 ± 9.6 years) or smoking status (four smokers in each group). One of the patients had a comorbid moderately severe social anxiety disorder and another one a comorbid dysthymia as well as a moderately severe generalized anxiety disorder. The study was approved by the local ethics committee and all subjects gave their written informed consent.

2.2. Cognitive behavioural therapy and psychometric assessment

Patients (not controls) received eight sessions in 90 min of cognitive behavioural therapy in a group setting (two subsequent groups with five participants) within one month. The therapy was standardized, based on a manual (Margraf and Schneider, 1990) and conducted by a certified psychologist accompanied by a co-therapist. It contained elements of education, interoceptive exposure, preparation for in-vivo exposure, stress management, relaxation therapy and cognitive restructuring. Before the beginning of therapy, after therapy, one month and five months after the end of therapy, clinical severity assessments were performed by employment of the Panic and Agoraphobia Scale (Bandelow, 1995), the Mobility Index, alone and accompanied (Chambless et al., 1985), the Beck Anxiety Inventory (Beck and Steer, 1993) and the Beck Depression Inventory (Beck and Steer, 1988).

2.3. Exposure therapy and blood collection

Three individual therapist-guided in-vivo exposure sessions per patient took place, with one exposure session weekly in the weeks 2–4 of therapy. The three therapists were two thoroughly exposure-trained medical students and a certified psychologist with an additional nursing qualification. We employed the *flooding* technique, starting with the most feared situation according to the individual fear hierarchy. Sessions with exposure therapy started in our clinic at 1 pm with the insertion of an indwelling venous catheter and the assessment of baseline blood and baseline fear (*Base 1*), the latter on a scale of 1 (no fear) to 10 (maximum fear). Subsequently, patient and therapist went to a place close to the individual exposure situation, where a second baseline assessment (blood and fear level; *Base 2*) was performed. At the moment of entering the phobic situation, the fear level was recorded (*Start*). Fear during exposure was monitored continuously every few

minutes and boosted by the therapist as much as possible by means of directing attention to phobic cues, by expressing phobic fears, by leaving the patient alone temporarily or by the instruction to hyperventilate if necessary to accelerate fear. After fear had reached its maximum (*Max*), we waited until it had decreased without any interference for at least two points, and then performed the next assessment of blood and fear level within the phobic situation (*During*). After fear had ceased completely, exposure was terminated (*End*). 5, 15, 30 and 60 min afterwards, the level of fear was assessed and blood collected (+5 min, +15 min, +30 min, +60 min). Accordingly, we recorded the fear level of the patients at 10 times and obtained seven blood samples. Blood was collected via the indwelling catheter without interrupting the therapeutic process, sitting or standing as required by the respective exposure situation. Matched control subjects went to the same places, where blood was taken and hyperventilation performed if required according to the exposure protocol of the respective patient.

2.4. Biochemical analyses

Samples were stabilized with 500KIE Aprotinin and 1.6 mg EDTA per ml blood and kept cold in ice during exposures and thereafter before centrifugation (10 min at 4000 rpm) and storage of plasma at -85°C . Plasma cortisol was analysed employing the radioimmunoassay DSL-2100[®] by Diagnostic Systems Laboratories (DSL, Webster, USA) and plasma ACTH by using the solid-phase, two-site sequential chemiluminescent immunometric assay Immulite[®]2000 (Siemens Medical Solutions Diagnostics, Los Angeles, USA). Intra- and inter-assay variabilities were 8.4–11.1% and 8.9–11.5% for cortisol and 6.7–9.5% and 6.1–10% for ACTH.

2.5. Statistical analysis

Hormonal data were subject to a logarithmic (lg 10) transformation in order to improve data distribution. The outcome of psychotherapy was analysed with repeated-measures ANOVA's with *Time* (Baseline, Post-Therapy, +1 Month, +5 Months) as the within-subjects factor. The course of stress hormones within and between exposures in comparison of patients and controls was analysed employing a 3-factorial ANOVA with *Time* (Base 1, Base 2, During, +5 min, +15 min, +30 min, +60 min) and *Exposure* (Expo 1, Expo 2, Expo 3) as within-subjects factors and *Group* (Patients, Controls) as the between-subjects factor. The course of fear levels within and between exposures in the two groups were analysed in an analogous manner, with the only difference that the factor *Time* included 10 time points (Base 1, Base 2, Start, Maximum, During, End, +5 min, +15 min, +30 min, +60 min). Sphericity was analysed by Mauchly testing and degrees of freedom adjusted if $p < 0.10$. Post-hoc tests were corrected for multiple testing (Bonferroni).

For correlations of stress hormone concentrations and fear during exposure with psychopathology, means of cortisol and ACTH levels were calculated from the respective seven hormone values of one exposure and means of VAS values from the respective 10 VAS values of one exposure. As a measure of main therapy outcome for these correlation analyses, data of the most relevant psychopathological measure (Panic and Agoraphobia Scale) were transferred into percentages of the respective baseline scores, i.e. low values represent high therapy success. Correlations were performed employing Pearsons Product-Moment Correlations as well as non-parametrical Kendall's Tau rank correlations. In face of the relatively high number of correlations calculated on a low number of patients, in this exploratory correlation analysis we abstained from adjustment for multiple testing and interpret the results with caution. Statistical significance was accepted if $p < 0.05$.

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