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A combined dexamethasone/corticotropin-releasing hormone test in patients with chronic PTSD – First preliminary results

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Abstract

Background: Reports about alterations of hypothalamic-pituitary-adrenocortical (HPA) function in patients with chronic posttraumatic stress disorder (PTSD) are inconsistent and controversial. More refined laboratory tests and subgrouping of PTSD patients might help to decrease variance of findings.
Methods: 14 subjects with chronic PTSD and 14 healthy controls were examined between 13:00 and 17:00 using a modified combined dexamethasone/CRH test (0.5 mg dexamethasone at 23:00, 100 μg CRH at 15:00). Plasma adenocorticotropic hormone (ACTH), cortisol and blood pressure were measured every 15 min from 14:45 until 17:00.
Results: No significant differences between patients and controls were found in the analyses of ACTH and cortisol levels, but a significantly elevated systolic and diastolic blood pressure in PTSD. Severity of depressive symptoms had no influence. However, explorative analyses showed that patients with a history of childhood traumatization had significantly higher post-dexamethasone-ACTH levels and a significantly lower diastolic blood pressure in comparison to patients without early trauma.
Conclusions: In this first pilot study in a typical clinical sample of patients with chronic PTSD we found effects of severe adverse events in childhood on HPA axis regulation. Maybe, childhood traumatization could influence HPA axis findings in PTSD. Further research is needed, especially dose-response studies with different doses of dexamethasone in dexamethasone/CRH tests in PTSD.

Keywords: Posttraumatic stress disorder; Dexamethasone/CRH test; HPA axis; Childhood trauma; ACTH; Cortisol

1. Introduction

Current data for alterations of HPA axis activity in posttraumatic stress disorder (PTSD) are inconsistent and controversial (Yehuda, 2002; Rasmusson et al., 2003). Although most studies show evidence for increased hypothalamic corticotropin-releasing hormone (CRH), reduced peripheral cortisol levels, and enhanced glucocorticoid receptor mediated negative feedback at the pituitary, these findings are somewhat equivocal. Maybe, this variance is partly due to different subtypes of PTSD or to insufficiently elaborate endocrine probes.

In major depression, development of the combined dexamethasone/CRH test has greatly increased sensitivity in comparison to previously used endocrine tests (Heuser et al., 1994). So far, no dexamethasone/CRH test data are available in PTSD. We modified the standard 1.5 mg dexamethasone/CRH test and used a low dose of dexamethasone (0.5 mg) to avoid putative floor effects, because hypersuppression even using this low dose of dexamethasone has been reported (Yehuda et al., 1993). Applying this modified low dose dexamethasone/CRH test, we hypothesized reduced ACTH and cortisol levels after dexamethasone and a lower increase after CRH in PTSD patients.

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Furthermore, we exploratively investigated the influence of depression and of a history of severe childhood abuse on dexamethasone/CRH test results.

2. Materials and methods

2.1. Subjects

In this pilot study we examined a typical clinical sample. Subjects were 14 patients with chronic PTSD (ten women, four men, mean age = 38.9 years, range = 22–57, mean body mass index (BMI) = 25.3 kg/m^2) who had no psychotic, organic, or substance-related disorders, as assessed with the Structured Clinical Interview for DSM-IV (First et al., 1996) and 14 healthy sex- and age-matched controls (mean age = 38.9 years, range = 21–59, mean BMI 23.1). All subjects had undergone a thorough medical examination including urinary drug screens. Healthy controls had no history of any psychiatric disorder as assessed by the MINI (Sheehan et al., 1998) and a psychiatric interview. The protocol was approved by the local ethics committee. Each participant provided written informed consent.

History of trauma was assessed by clinical exploration and the Posttraumatic Diagnostic Scale (PDS, Foa et al., 1997). Seven patients (six female, one male, mean age 33.9) were traumatized at age <12 years (childhood sexual or severe physical abuse). Seven patients (4 female, 3 male, mean age 43.6) reported no significant trauma at age <12 years. The PTSD qualifying events were sexual abuse/rapes ($n = 5$), accidents ($n = 3$), assaults ($n = 3$), and other reasons ($n = 3$: stillbirth, combat, torture). Mean duration of PTSD was 11.7 years (14.1 years in the group with childhood traumatisation (+CT)/9.25 years in the group without childhood traumatisation (−CT)). Mean severity of PTSD as per the PDS was 34.5 (range 16–47; +CT: range 16–42, mean 33.4; −CT: range 25–47, mean 35.6).

Ten patients (six female and four male) had a comorbid major depression. Mean severity of depression by the Beck Depression Inventory (BDI, Beck et al., 1961) was 27.8 (range 8–53; +CT: range 8–48, mean 26.6; −CT: range 18–53, mean 29).

Subjects were pre-treated orally with 0.5 mg of dexamethasone (Fortecortin^R, Merck, Darmstadt, Germany) at 23:00. On the next day they were studied in a single bedded quiet room in supine position. An intravenous catheter was inserted at 13:00 and kept open by 50 ml/h of 0.9% NaCl. At 15:00 subjects received 100 μg h-CRH (Clinalfa, Laeufelfingen, Switzerland). Blood samples were obtained every 15 min from 14:45 until 17:00. Blood pressure was registered simultaneously with an automatic device. Blood was placed on ice, plasma was separated and aliquots stored at −80°C until analyses.

Plasma concentrations of ACTH and cortisol were determined using commercial immunoradiometric and radioimmunoassays (ICN Biomedicals, Carson, CA; Nichols Institute, San Juan Capistrano, CA). Inter- and intrassays coefficients of variation were below 8%. Detection limits were 0.5 μg/dl for cortisol and 2 pg/ml for ACTH.

2.1.1. Statistical analyses

Effects of groups and subgroups on ACTH and cortisol time concentration curves and blood pressure as well were evaluated for four indicators (mean baseline post-dexamethasone levels (average of values at 14:45 and 15:00), post-CRH area under the curve, post-CRH mean location (average of values between 15:00 and 17:00), and post-CRH maximal change of hormone concentrations) using for each of the hormones and blood pressure parameters a multivariate analysis of variance (MANOVA). As covariates we respectively considered BMI, mean arterial blood pressure, age, BDI, and PDS. When significant group effects were found, univariate F-test followed to identify the indicators which contribute significantly. As nominal level of significance, $\alpha = 0.05$ was accepted. All post-hoc tests (univariate F-Tests) were performed at a reduced level of significance (Bonferroni procedure) to keep the type I error less or equal to 0.05. All values are given as mean ± SEM.

3. Results

3.1. PTSD patients vs. healthy controls

We did not find any statistically significant group effect between patients and controls in the analyses of ACTH (time concentration curve: please see Fig. 1) and cortisol curve indicators.

However, in post-hoc tests there were significant group differences in baseline post-dexamethasone systolic blood pressure (PTSD vs. controls: 125.7 ± 5.6 mm Hg vs. 109.5 ± 2.8; $F(1,26) = 6.67$, $p < 0.05$) and diastolic blood

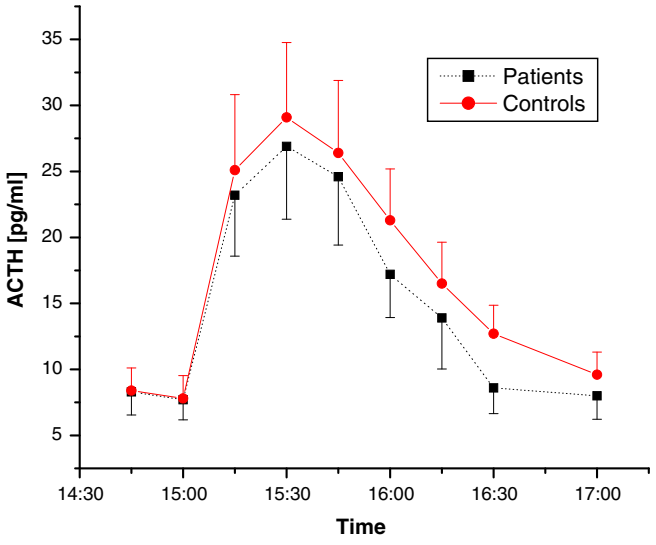

Fig. 1. ACTH values in 14 PTSD patients and 14 controls. Values are means ± SEM.