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Cortisol has enhancing, rather than impairing effects on memory retrieval in PTSD

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Summary
Background: In the present study, we aimed to compare the effect of exogenous cortisol on memory retrieval in posttraumatic stress disorder (PTSD) with the effects in healthy controls. In healthy participants, administration of cortisol impairs declarative memory retrieval. Only a few studies have investigated these effects in PTSD yielding mixed results.
Methods: In a placebo-controlled crossover study, 44 patients with PTSD and 65 healthy controls received either placebo or 10 mg of hydrocortisone orally before memory testing. In addition to declarative memory retrieval (word list learning), we also tested autobiographical memory retrieval specificity.
Results: In both tasks opposing effects of cortisol on memory were observed when comparing patients with controls. In controls, cortisol had impairing effects on memory retrieval, while in PTSD patients cortisol had enhancing effects on memory retrieval in both memory domains.
Conclusions: The present results suggest beneficial effects of acute cortisol elevations on hippocampal mediated memory processes in PTSD. Possible neurobiological mechanisms underlying these findings are discussed.

1. Introduction

In posttraumatic stress disorder (PTSD), in contrast to major depressive disorder (MDD), reduced basal cortisol levels and enhanced negative feedback of the hypothalamus pituitary adrenal (HPA) axis are prominent findings (Yehuda, 2002). These results have often been interpreted in the context of

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enhanced glucocorticoid receptor (GR) sensitivity (Yehuda, 2009; Rohleder et al., 2010). In addition to a more pronounced cortisol suppression even after a low dose of dexamethasone, changes in number and responsiveness of GR have been reported (Yehuda et al., 2004). However, there are also contradictory findings (Pace et al., 2012). A meta-analysis revealed that gender as well as type of trauma plays a role in HPA axis dysregulation in PTSD (Meewisse et al., 2007). Low cortisol has been found predominantly in patients with PTSD due to sexual or physical abuse. Comorbid major depressive disorder might also be relevant (de Kloet et al., 2008).

Neuropsychological alterations are also an important feature in PTSD. Problems particularly with learning and memory have been found, including deficits in verbal declarative memory as well as autobiographical memory, i.e. overgeneralized autobiographical memory retrieval (Buckley et al., 2000; Golier and Yehuda, 2002; Schonfeld and Ehlers, 2006). Patients with overgeneralized memory have difficulties in retrieving specific autobiographical events; instead, they tend to reply with abstract or general memory content (e.g. they summarize several different events).

In healthy humans, most studies suggest impairing effects of glucocorticoids on memory retrieval, especially hippocampus based declarative memory retrieval, while consolidation seem to be improved by glucocorticoids (Wolf, 2003, 2009; Het et al., 2005; de Quervain et al., 2009). Up to now, studies that investigate the effects of cortisol administration or stress exposure on memory in patients with PTSD are rare and yielded inconclusive results (Bremner et al., 2004; Grossman et al., 2006; Yehuda et al., 2007, 2010). However, none of these studies focused on memory retrieval, but instead administered cortisol before memory encoding and thus are unable to separate the effects of cortisol on acquisition, consolidation and retrieval. This might be one reason for the conflicting results. In PTSD, one study reported stronger negative effects of hydrocortisone treatment on declarative memory (Grossman et al., 2006), which is in line with the hypotheses of an enhanced GR sensitivity in patients suffering from PTSD (Vythilingam et al., 2006). In older PTSD patients opposing effects have been reported, namely a more pronounced enhancement of declarative memory performance (Yehuda et al., 2007). However, findings are equivocal (Yehuda et al., 2010). Importantly, sample sizes of these previous studies were rather small thus limiting the conclusions that can be drawn. Furthermore, most participants in these studies were male and two of the three studies investigated war veterans. However, PTSD is more prominent in women and, therefore, it would be of great interest to study also female patients.

Major depression is also characterized by cognitive impairments and HPA axis dysregulations, however in this disorder reduced rather than enhanced GC sensitivity has been observed (Holsboer, 2000; Rohleder et al., 2010) accompanied by HPA hyperactivity. It thus might be of interest to compare the effects of cortisol administration on memory between the two disorders. In a series of studies with patients suffering from major depressive disorder, we investigated the effects of 10 mg hydrocortisone in different memory domains. In line with the literature, hydrocortisone treatment impaired declarative memory retrieval, working memory, and autobiographical memory specificity in healthy controls (Schlosser et al., 2010; Terfehr et al., 2011a,b). In contrast, these impairing effects were not observed in MDD patients. We suggested that the lacking effect of acute cortisol elevations on memory might be due to reduced functioning of hippocampal and/or prefrontal GRs in those patients (Schlosser et al., 2011; Wingenfeld and Wolf, 2011).

In the present study, we aimed to further investigate the effect of exogenous cortisol on declarative and autobiographical memory performance in PTSD. For the first time in PTSD patients, we used a study design which specifically investigates memory retrieval. Based on the results of Grossman (Grossman et al., 2006) and the hypothesis of enhanced GR sensitivity in PTSD (Yehuda et al., 2004, 2006), it could be assumed that hydrocortisone would lead to a stronger memory retrieval impairment in patients with PTSD. However, based on previous studies reporting memory enhancing properties of cortisol in PTSD patients (Yehuda et al., 2007) and initial observations of beneficial effects of cortisol treatment on PTSD symptoms (Aerni et al., 2004), the opposite prediction (enhanced memory retrieval after cortisol administration) appeared equally likely.

2. Methods and materials

2.1. Participants

44 patients with PTSD and 65 healthy controls aged of 18 years or older (range 20—58 years) participated in our study (see Table 1). In the PTSD there were 38 women and six men, while the control groups consisted of 42 women and 23 men. Fifty-one of the control participants were part of a former study by our working group (Terfehr et al., 2011a). Patients were recruited at the Department of Psychiatry and Psychotherapy Bethel (Ev. Hospital Bielefeld, Germany), and at the Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Germany.

Participants were excluded if they had any of the following current or previous medical conditions: CNS relevant somatic diseases or severe somatic diseases (e.g. neurological diseases), metabolic diseases (e.g. thyroid disease, diabetes), organic shift in cortisol secretion (e.g. Cushings syndrome), immune-mediated diseases, medicated hypertension, or current infections. Further exclusion criteria were pregnancy, current anorexia, current or lifetime schizophrenia, alcohol or drug dependence, bipolar disorder, schizoaffective disorder, major depression with psychotic symptoms, attention deficit hyperactivity disorder or cognitive impairment. Intake of antidepressants did not lead to exclusion.

Written informed consent was obtained from all participants. Healthy participants were recruited by local advertisement and received financial remuneration for their efforts (100€). The study was approved by the University of Muenster Ethics Committee and the Ethics Committee of the Medical Council of Hamburg.

2.2. Procedure

To assess psychiatric diagnoses participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I and II