Psychoneuroendocrinology (2014) 40, 151—158

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Cortisol response to cosyntropin administration in military veterans with or without posttraumatic stress disorder

Julia A. Golier [a,b,*], Kimberly Caramanica [a], Iouri Makotkine [a,b], Leo Sher [a,b], Rachel Yehuda [a,b]

[a] Departments of Psychiatry, James J. Peters VA Medical Center, Bronx, NY, United States
[b] Mount Sinai School of Medicine, New York, NY, United States

Received 4 June 2013; received in revised form 16 October 2013; accepted 23 October 2013

KEYWORDS
Post-traumatic stress disorder (PTSD);
Veterans;
Cosyntropin;
Cortisol;
ACTH

Summary Studies have demonstrated altered sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis to its direct regulators in veterans with posttraumatic stress disorder (PTSD), but little is known about the adrenal response to hormonal stimulation in PTSD. An increased cortisol response to synthetic corticotropin-releasing factor (CRF) was recently found to be associated with war-zone deployment and not PTSD specifically. To more accurately assess whether there is altered adrenocortical responsivity to hormonal stimulation in relation to war-zone deployment or PTSD, we performed the low-dose cosyntropin stimulation test in a sample of 45 male veterans: 13 war-zone exposed veterans with chronic PTSD (PTSD+), 22 war-zone exposed veterans without chronic PTSD (PTSD-), and 10 veterans not exposed to a war-zone and without chronic PTSD (non-exposed). Plasma cortisol and ACTH were measured at baseline and at intervals over a one hour period following intravenous administration of 1 μg of cosyntropin. A significant main effect of group (PTSD+, PTSD—, non-exposed) on the cortisol response to cosyntropin was observed. Cosyntropin-stimulated plasma cortisol levels were significantly higher in the PTSD+ and PTSD— groups compared to the non-exposed group. A significant main effect of group was also observed on peak cortisol levels. These findings suggest that war-zone exposure itself has persistent effects on adrenocortical activity.
Published by Elsevier Ltd.

1. Introduction

Increasing evidence suggests that long-term alterations in hypothalamic-pituitary-adrenal (HPA) axis activity are associated with stress and posttraumatic stress disorder (PTSD), and that these changes play an important role in the pathophysiology of PTSD. HPA axis function in veterans with PTSD appears to be more susceptible to both stimulatory and

* Corresponding author at: James J. Peters VA Medical Center, OOMH; 130 West Kingsbridge Road, Bronx, NY 10468, United States. Tel.: +1 718 584 9000x5196; fax: +1 718 741 4775.
E-mail address: julia.golier@va.gov (J.A. Golier).

0306-4530/$ — see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.psyneuen.2013.10.020

inhibitory influences by its hormonal regulators; indeed, exaggerated cortisol levels have been found in response to stress challenges (Bremner et al., 2003; Elzinga et al., 2003). There is also consistent evidence for increased suppression of cortisol and adrenocorticotropic hormone (ACTH) to the synthetic glucocorticoid dexamethasone (DEX) (Yehuda et al., 1993, 1995; de Kloet et al., 2007). Acute administration of synthetic glucocorticoids has also been linked with exaggerated effects on learning and memory - both deleterious and beneficial (Grossman et al., 2006; Vythilingam et al., 2006; Yehuda et al., 2007). In peripheral assays, enhanced glucocorticoid sensitivity of lysozyme activity (Yehuda et al., 2004) and inflammatory cytokine production (Rohleder et al., 2004) has been described.

Given that altered glucocorticoid sensitivity has been described in multiple target systems in PTSD, it is important to understand the factors that impact glucocorticoid release in this disorder and to characterize the full range of regulatory influences that impact HPA axis activity in PTSD. Studies of the effects of corticotropin-releasing factor (CRF) stimulation on cortisol and ACTH release in PTSD have shown mixed results. An initial study in veterans showed a reduced ACTH and cortisol response in combat veterans with chronic PTSD compared to normal volunteers (Smith et al., 1989); an exaggerated ACTH and cortisol response was found in premenopausal women with PTSD compared to healthy non-traumatized subjects (Rasmusson et al., 2001). In response to human corticotropin-releasing hormone (CRH), no difference in ACTH or cortisol was found in PTSD patients compared to healthy controls (Kellner et al., 2003).

More recently, war-zone deployed veterans with and without PTSD showed an enhanced cortisol response to CRF compared to non-exposed veterans, suggesting a role of combat exposure in HPA axis reactivity (Golier et al., 2012). However, since there were also effects of military cohort on the ACTH response to CRF, it is not possible to isolate the effect of CRF on cortisol. Therefore, the cortisol response to direct stimulation with cosyntropin was examined to allow for a direct assessment of the adrenal response to pharmacologic manipulation (Magnotti and Shimshi, 2008; Hamilton and Cotton, 2010) in male war-zone exposed veterans with and without PTSD and non-exposed veterans without PTSD. The low-dose (1 μg) cosyntropin test (α 1-24 corticotropin, a synthetic subunit of ACTH) was used rather than the conventional-dose short test (250 μg), as we hypothesized that veterans with PTSD would have an enhanced cortisol response to cosyntropin based on the evidence of increased HPA axis sensitization in PTSD, including emerging molecular evidence of altered glucocorticoid sensitivity in PTSD (Binder et al., 2008; Yehuda et al., 2009).

2. Methods

2.1. Subjects

This study was approved by the institutional review boards (IRBs) of the Bronx VA Medical Center and the Mount Sinai School of Medicine. 13 male war-zone exposed veterans with chronic PTSD (PTSD+) (6 Vietnam era veterans, 3 Gulf War era veterans, 4 OIF/OEF era veterans), 22 male war-zone exposed veterans without chronic PTSD (PTSD−) (12 Vietnam era veterans, 7 Gulf War era veterans, 3 OIF/OEF era veterans), and 10 male veterans not exposed to a war-zone and without chronic PTSD (non-exposed) (4 Vietnam era veterans, 3 Gulf War era veterans, 3 OIF/OEF era veterans) were studied. Subjects were recruited through print advertising, clinical referral, and flyers in the Bronx VA Medical Center.

2.2. Clinical evaluations

After providing written informed consent, subjects underwent a complete medical and psychiatric examination including administration of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) and the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995). Subjects who had a major medical or neurological illness, a lifetime history of schizophrenia, bipolar disorder or obsessive-compulsive disorder, current alcohol or substance abuse/dependence, who were morbidly obese (BMI $>$ 40), smoked an average of more than 2 packs of cigarettes/day, or who were taking steroids, anti-histamines, opioids, oral hypoglycemic agents, insulin, or psychiatric medications were excluded. More than two-thirds of study participants were not taking any medication; the most commonly reported medications taken were non-opioid analgesics, anti-hypertensives, lipid-lowering medications, and proton-pump inhibitors. Participants with a history of previous hypersensitivity reactions to ACTH or with a history of allergic illnesses were also excluded.

Self-reported environmental and combat exposures were obtained based on questionnaires developed for use in the study of Gulf War veterans (Rosenheck, 1992; Wolfe et al., 2002). Participants also completed the Combat Exposure Scale (CES), a 34-item self-report questionnaire (Lund et al., 1984) and the Expanded Health Symptoms Checklist which inquires about health symptoms in nine domains (cardiac, dermatologic, musculoskeletal, gastrointestinal, genitourinary, neurological, neuropsychological, psychological, and pulmonary) (Proctor et al., 1998).

2.3. Cosyntropin Administration Test

The low-dose cosyntropin stimulation test was performed at the General Clinical Research Center (GCRC) at the Mount Sinai School of Medicine. Subjects were asked to have a light breakfast at 8:00 a.m. and to refrain from eating until after the procedure upon admission to the outpatient GCRC. After placement of an indwelling venous (i.v.) catheter and 30 min of accommodation, blood samples were drawn at time −30 and 0 min, following which 1 μg of cosyntropin (Cortrosyn®, Organon) was administered as an i.v. bolus at approximately 2:00 p.m. Blood was drawn at +10, 20, 30, 40, and 60 min and analyzed for cortisol and ACTH. For some subjects dehydroepiandrosterone (DHEA) (n = 28) and cortisol binding globulin (CBG) (n = 13) were measured at +0, 30, 60, and 90 min. Frequent sampling points were used to ensure that peak cortisol values were captured, as the peak cortisol level can occur earlier or later than the 30 min interval typically used for the standard test.

Blood samples for hormonal analysis were collected in EDTA containing tubes, placed on ice, and spun at 400 × g in 4 °C. After centrifugation, plasma was separated from the rest of the blood and immediately frozen at −70 °C until