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Pre-treatment cortisol awakening response predicts symptom reduction in posttraumatic stress disorder after treatment

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ABSTRACT

Dysfunction of the HPA-axis has frequently been found in the aftermath of trauma exposure with or without PTSD. Decreasing HPA-axis reactivity to different stress cues has been reported during PTSD treatment. The cortisol awakening response (CAR_i) is a well-validated, standardized measure of HPA-axis reactivity which can be easily acquired in the clinical setting. Whether CAR_i changes over time in traumatized individuals are specific to PTSD treatment is unknown. Furthermore, a possible role for the baseline CAR_i in predicting symptom reduction after treatment in PTSD has not been examined before. To answer these questions, a cohort study was conducted in which the awakening cortisol was measured in both PTSD (N = 41) and non-PTSD (N = 25) combat-exposed male subjects. Measurements took place at inclusion and 6–8 months after inclusion for both the PTSD and the non-PTSD group. During the 6–8 months interval, PTSD patients received trauma-focused focused psychotherapy, whereas non-PTSD patients received no treatment. We found a decrease in the CAR_i over time in both groups, suggesting it was not specific to PTSD or the effect of treatment. Therefore, caution is warranted when attributing diminished HPA-axis reactivity over time to effects of PTSD treatment. Second, CAR_i prior to treatment predicted PTSD symptom reduction (CAPS score change) after treatment, and accounted for 10% of the variance, even when adjusted for changes in depressive symptoms and medication use during the study period. A putative role emerges for CAR_i as a predictive biomarker of symptom reduction in male individuals with combat-related PTSD.

1. Introduction

Following trauma exposure vulnerable individuals develop posttraumatic stress disorder (PTSD), a trauma and stress related disorder with intrusive and re-experiencing symptoms, avoidance, and negative changes in cognition (American Psychiatric Association, 2013) characterized by a broad range of abnormal stress reactions (e.g.,intrusive and re-experiencing symptoms, avoidance, physiological hyperarousal, and negative changes in cognition) (American Psychiatric Association, 2013). The hypothalamic-pituitary-adrenal axis (HPA-axis) has received particular attention in PTSD research, because it represents the organism's major neuroendocrine stress response system (Heim and Nemeroff, 2009). Although not thoroughly consistent, some HPA-axis alterations have been reproduced in several studies in individuals with PTSD, such as: low 24-h urinary cortisol, low daily cortisol secretion during early morning, increased glucocorticoid receptors on lymphocyte cell membranes and enhanced HPA-axis sensitivity to feedback inhibition. Moreover, some studies found that baseline urinary (Baker et al., 1999), plasma (Goenjian et al., 2003) and salivary cortisol concentrations (Wahbeh and Oken, 2013) were related to the severity of PTSD symptoms. A recent review of prospective studies focusing on psychobiological predictors of PTSD in the acute aftermath of traumatic stress showed that lower peritraumatic cortisol levels were associated with increased risk for PTSD (Morris and Rao, 2013). Other meta-analytic evidence for HPA-axis alterations have been described by Morris et al. (2012), as well as by Meewisse et al. (2007). The HPA axis shows a dynamic ultraradian rhythm that is manifested by fluctuating levels of ACTH and glucocorticoids (Walker et al., 2012). Fluctuations in glucocorticoid levels are necessary to maintain homeostasis, and may thus be indicative of treatment response.

Only a few studies have recently addressed the question whether treatment success in PTSD may be associated with changes in cortisol

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secretion, and they mainly assessed the HPA-axis function before and after trauma-focused therapy. According to international guidelines (National Institute for Health and Care Excellence, 2005), trauma-focused therapy is the most effective treatment available in PTSD. Trauma-focused therapy includes trauma-focused cognitive behavioral therapy (tf-CBT), eye movement desensitization and reprocessing (EMDR) and other related psychological treatments with the following common components: psychoeducation, imaginal exposure, cognitive processing and cognitive restructuring. Rothbaum et al. (2014) found a decrease in the salivary cortisol response to virtual exposure therapy over time, which was more evident when D-cycloserine was administered during the session. This finding has been recently reproduced by Norrholm et al. (2016), although the type of medication administered during the therapy sessions was no longer of influence. Others (Gerardi et al., 2010) found diminished cortisol reactivity after successful exposure therapy. It has been suggested that these results may reflect decreased HPA-reactivity to reminders of the stressor in response to treatment. In addition, Olff et al. (2007) reported an increase in the basal morning cortisol at the end of treatment in individuals with PTSD remission, as opposed to decrease in non-responders. This discrepancy may be explained by the fact that the latter study employed only one single morning sample as an estimate of the basal cortisol output, while the previous studies measured cortisol response to trauma cues as estimate of HPA-axis responsivity.

While paradigms of trauma cue exposure are difficult to standardize, single cortisol sample measurements have poor ecological validity and are prone to intra-individual variability (Stalder et al., 2015). These problems can be avoided by using the cortisol awakening response (CAR) as a well-validated measure of HPA-axis function (Stalder et al., 2015). The CAR captures information on both basal activity and reactivity of the HPA-axis without introducing an experimental stressor (Fekedulegn et al., 2015). The basal ascending morning cortisol output can be estimated by the area under the ground with respect to 0 (CAR_g, g = ground) while the superimposed response to awakening is estimated as the area under the curve relative to waking values (CAR_i, i = increase). To our knowledge, only one study has examined changes in both CAR indices following successful treatment in PTSD, up to now (Pacella et al., 2014). In a community sample with chronic PTSD, the remission or persistence of PTSD was not significantly related to CAR_i at 10 weeks of psychotherapeutic or pharmacological treatment.

Furthermore, CAR_i did not change between the pre- to post-treatment assessment in male responders, whereas the female responders displayed lower CAR_i post-treatment than female non-responders. The specificity of the findings for PTSD and for the PTSD treatment has not yet been tested. Earlier literature showed that trauma exposure per se, in the absence of a PTSD diagnosis (de Kloet et al., 2007; Meewisse et al., 2007), as well as time passed since trauma, regardless of treatment (Morris et al., 2012), can also induce detectable changes in the CAR. More specifically, a blunting of the HPA-axis responsivity, and thus CAR_i, can be expected in the aftermath of traumatic exposure, regardless of the PTSD diagnosis and PTSD treatment status.

Objective biomarkers of treatment efficacy are highly needed in guiding treatment choice in PTSD, considering the high rates of symptom persistence after treatment (Bradley et al., 2005). CAR_g was proved not to be predictive of treatment effect in two recent clinical trials including trauma-focused therapy (Rauch et al., 2015; Nijdam et al., 2015). On the other hand, a positive relationship existed between symptom reduction and the HPA-axis responsivity in the form of suppression of the CAR by dexamethasone challenge (Nijdam et al., 2015) or activation by script-driven imagery (Rauch et al., 2015). Similarly, Pacella et al. (2014) observed in their preliminary analysis a higher cortisol response to awakening (CAR_i) at baseline that was associated with lower PTSD symptoms post-intervention (Pearson's $r = -0.36$, $p < 0.10$). However, no measure of pre- to post-treatment improvement in PTSD symptomatology was assessed.

We present here a prospective, observational study exploring the cortisol awakening response and its association with clinical outcome during trauma-focused therapy in men with combat-related PTSD, while accounting for trauma exposure among other confounds. To this purpose, patients with combat-related PTSD, and combat-exposed, healthy individuals, were assessed at a fixed time interval of six months. This study is part of a larger cohort study on biological and psychological aspects of recovery following PTSD treatment in the Dutch Armed Forces. The first research question was whether there were changes in CAR after 6 months of trauma-focused psychotherapy. We expected to find lower CAR after 6 months in both combat exposed groups (with and without PTSD) and that this effect would be stronger for patients with PTSD that received the trauma focused psychotherapy. The second research question that was investigated was whether CAR at the beginning of the treatment can serve as a predictor of symptom change during treatment for PTSD. In the present study, we specifically tested the hypothesis that CAR_i, as a well validated estimate of HPA-axis responsivity, would positively predict the extent of clinical improvement in PTSD.

2. Methods

2.1. Participants

Study subjects were participants of an observational longitudinal study, which was conducted between September 2010 and September 2013. Cortisol data were available in 42 male subjects with combat-related PTSD (patients) and 25 male veterans without PTSD (combat controls). PTSD patients were veterans as well as active duty personnel recruited from one of four outpatient clinics of the Military Mental Healthcare Organization. PTSD was diagnosed by a clinician according to the DSM-IV criteria (American Psychiatric Association, 2000). Control participants were recruited via advertisements. At the time of inclusion, all PTSD patients had current PTSD, no current alcohol or substance dependence, and no neurological disorder. Combat controls had no clinical PTSD symptoms (CAPS < 15, see Section 2.2), no current psychiatric disorder, no alcohol or substance dependency, no neurological disorder, and no lifetime PTSD. All participants had been deployed at least once for a period of at least 4 months.

Participants received monetary compensation for participation (€12.50 per hour). Written informed consent was obtained from all participants after they had received a complete written and verbal explanation of the study, in accordance with procedures approved by the University Medical Center Utrecht ethics committee and the Declaration of Helsinki.

2.2. Psychological instruments

At study inclusion (T_0) and 6–8 months later (T_1), all participants were repeatedly assessed for psychiatric symptoms with several clinical interviews and self-report scales.

The PTSD diagnosis and severity were confirmed by a clinician or trained researcher using the Clinician-Administered PTSD Scale-IV (CAPS; Blake et al., 1995). This semi-structured interview, designed to assess DSM-IV symptoms of PTSD, is the gold standard PTSD instrument in the field and has good psychometric properties (Weathers et al., 2001). A PTSD case was identified if subjects endorsed the requisite DSM-IV symptoms at least at a frequency of 1 and at an intensity of 2 (Weathers et al., 2001). The threshold for the PTSD diagnosis was a minimal CAPS score of 45. Participants were included in the combat control group when the total CAPS score was 15 or lower. The *Structured Clinical Interview for DSM-IV* (SCID; First et al., 1996) was administered to assess co-existing psychopathology.

Besides PTSD, depression has been related to an excessive daily cortisol secretion and a blunted sensitivity of the HPA-axis (Wingenfeld and Wolf, 2015). *The Mood and Anxiety Symptoms Questionnaire* (MASQ; de Beurs et al., 2007) is a self-report inventory that is particularly useful