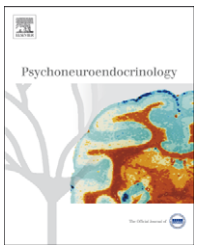
Psychoneuroendocrinology (2007) 32, 619–626

Available at www.sciencedirect.com

ScienceDirect

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



Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD ☆

Miranda Olff[a,*], Giel-Jan de Vries[a], Yener Güzelcan[a,b], Johanna Assies[c], Berthold P.R. Gersons[a]

[a]*Center for Psychological Trauma, Department of Psychiatry, Academic Medical Center/de Meren, University of Amsterdam, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands*
[b]*Mental Health Care Department of 's Hertogenbosch and Department of Psychiatry, Academic Medical Center, University of Amsterdam, , Amsterdam, The Netherlands*
[c]*Department of Psychiatry, Academic Medical Center/ de Meren, Amsterdam, The Netherlands*

Received 15 November 2006; received in revised form 30 March 2007; accepted 4 April 2007

KEYWORDS
Post-traumatic stress disorder;
Psychotherapy;
Hypothalamus–pituitary–adrenal (HPA) axis;
Hypothalamus–pituitary–thyroid (HPT) axis;
Cortisol;
TSH;
Depression

Summary
Post-traumatic stress disorder (PTSD) has been associated with dysregulation of the neuroendocrine system. In this study we examine the effects of psychotherapy in 21 PTSD patients, with and without coexisting depression, on the levels of six stress-related hormones: cortisol, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone-sulfate (DHEA-S), prolactin, thyrotropin (TSH) and free thyroxin (fT4). The results show that after brief eclectic psychotherapy (BEP) significant changes occurred in levels of cortisol and DHEA. Responders showed an increase in cortisol and DHEA levels, while in non-responders both hormone levels decreased. Differences were only found after controlling for depressive symptoms. In conclusion, effective psychotherapy for PTSD may alter dysregulations in the Hypothalamus–pituitary–adrenal (HPA)-axis, but comorbid depressive symptoms should be taken into account.

1. Introduction

Several studies have shown alterations of the hypothalamic–pituitary–adrenal (HPA) axis in individuals with post-traumatic stress disorder (PTSD). Basal plasma, awakening saliva and 24-h urinary cortisol values have been found to be lower in subjects with PTSD than in healthy individuals with or without exposure to trauma (Yehuda et al., 1995; Rohleder et al., 2004). However, there are also studies indicating no differences in cortisol levels (Baker et al., 1999; Rasmusson et al., 2001; Altemus et al., 2003) or even higher levels (Pitman and Orr, 1990; Lemieux and Coe, 1995; Lindley et al., 2004) of cortisol in PTSD. Differences may be related to gender and the nature of the trauma (Olff et al.,

☆Parts of this paper have been presented at the 20th Annual Meeting of International Society for Traumatic Stress Studies. New Orleans, 2004.

*Corresponding author. Tel.: +31 20 5662356; fax: +31 20 6919019.
E-mail address: M.Olff@amc.uva.nl (M. Olff).

0306-4530/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2007.04.001

2007; Meewisse et al., in press). Another hormone produced by the adrenal cortex is dehydroepiandosterone (DHEA) as well as its sulfate ester (DHEA-S), together called DHEA(S). It has been suggested that DHEA can block or inhibit corticosteroid action (Kalimi et al., 1994; Spivak et al., 2000). The anti-glucocorticoid properties of DHEA may contribute to an upregulation of HPA-axis responses as well as mitigate possible deleterious effects of high cortisol levels on the brain in PTSD (Rasmusson et al., 2003). Few studies have been performed on DHEA(S) in PTSD patients, with results indicating higher DHEA levels (Spivak et al., 2000; Sondergaard et al., 2002).

In addition to studies on changes in the HPA-axis, studies have been conducted on other hormone values observed in various HPA-axis-related psychiatric disorders like prolactin, thyrotropin (TSH), and free thyroxin (fT4). The hypothalamic–pituitary–thyroid (HPT) axis has received little attention in traumatic stress research, although Mason (1968) had already demonstrated the relationship between traumatic stress and thyroid function as had Wang and Mason (1999).

In our cross-sectional study (Olff et al., 2006a) we found lower cortisol levels in PTSD patients compared with healthy controls. Interestingly, we also found that cortisol levels were related to the severity of PTSD symptoms as was also found in other studies (Baker et al., 1999; Goenjian et al., 2003). Symptom improvement following treatment might therefore be associated with changes in cortisol levels. The present study provides an opportunity to examine biological correlates of symptom improvement after psychotherapy.

Until now, very little is known about the effects of treatment—psychological or pharmacological—on hormone levels in PTSD. Few studies have investigated neuroendocrine changes associated with pharmacological treatment. Tucker et al. (2004b) examined the effects of citalopram and sertraline on cortisol in chronic PTSD, but found a complex relationship between neuroimmune and neuroendocrine systems with PTSD treatment. Paroxetine treatment of PTSD with comorbid depression did not change cortisol levels either (Tucker et al., 2004a). Rinne et al. (2003) treated female patients with borderline personality disorder and a history of childhood abuse with fluvoxamine and found it to reduce the hyper-responsiveness of the HPA-axis.

To our knowledge no systematic studies have been performed to examine the effects of psychological treatment on hormone levels in PTSD. Heber et al. (2002) described in a single case report the effects of eye movement desensitization and reprocessing (EMDR) on cortisol. After EMDR they found an increase in basal cortisol levels, and a more attenuated cortisol hypersuppression in response to the dexamethasone suppression test.

Trauma-focused CBT is mentioned as the most effective treatment for PTSD (Bradley et al., 2005; Gersons and Olff, 2005); see also guidelines of the National Institute of Clinical Excellence (2005, www.nice.org.uk). Brief eclectic psychotherapy (BEP) is a trauma-focused cognitive behavioral therapy (CBT) with some elements of psychodynamic therapy which has been shown to be effective in the treatment of PTSD (Gersons et al., 2000; Lindauer et al., 2005a). We have recently shown that this psychological treatment affects other psychobiological measures associated with symptom improvement in PTSD. In a recent functional brain imaging study we showed that symptom improvement was associated with changes in regional blood flow (Lindauer et al., 2005b). BEP modulated the functioning of specific PTSD-related sites in the prefrontal cortical regions. We also showed that successful psychotherapy normalized the heightened heart rate response to trauma imagery (Lindauer et al., 2006).

In the present study we examined whether recovery from PTSD following BEP was associated with changes in basal neuroendocrine levels. We evaluated six HPA- and HPT-axis-related hormone levels before and after psychological treatment. We hypothesized that with effective psychotherapy the low basal cortisol levels in PTSD patients would increase. To our knowledge this is the first study to assess the effects of psychotherapy in PTSD on these hormones.

2. Methods

2.1. Subjects

Twenty-one patients with chronic PTSD due to a type I civilian trauma, e.g. traffic accident, assault, medical event, work accident, loss of a loved one (time since trauma between 3 months and 5 years) were included. All patients were diagnosed with PTSD according to the DSM-IV classification system (American Psychiatric Association, (APA) 1994) and were included in the period from October 2002 to October 2003. Patients were selected from our outpatient unit and via newspaper advertisements. They were aged between 33 and 59 years.

Patients with past or present psychotic disorders, severe depressive disorders with psychotic symptoms or suicidal tendencies, bipolar disorders, psycho-organic syndromes and alcohol or drug addiction were excluded. They were also excluded from the study if suffering from a somatic illness known to cause endocrinological changes (asked by a self-report questionnaire as well as by structured interview). Psychotropic medication (i.e. anxiolytics and antidepressants) was allowed, but was to be held stable during the study period.

The study was approved by the Medical Ethical Committee of the Academic Medical Center. After complete description of the study, written informed consent was obtained.

2.2. Psychological instruments

The diagnosis of PTSD was based on DSM-IV criteria and was determined with the Structured Interview for Posttraumatic Stress Disorder (SI-PTSD; Davidson et al., 1989). For the Dutch version of the SI-PTSD, a Cronbach's alpha of 0.93 and a Cohen's kappa of 0.88 was found, which can be considered acceptable (Carlier et al., 1998). The Structured Clinical Interview for DSM-IV (SCID-I; Spitzer et al., 1995) was administered to assess co-existing psychopathology. The Dutch version of the Impact of Event Scale-Revised (IES-R; Creamer et al., 2003) was used to assess the severity of PTSD symptoms. The IES-R consists of a total score (Cronbach's alpha = 0.98) and three subscales: reexperiencing (Cronbach's alpha = 0.97), avoidance (Cronbach's alpha = 0.92), and hyperarousal (Cronbach's alpha = 0.95). The Beck Depression Inventory-II (BDI; Beck and Beamesderfer, 1974)

a widely used valid and reliable instrument to assess depression was used to assess the severity of depressive symptoms.

2.3. Hormones

Routine somatic screening was performed on the PTSD patients and on the healthy comparison group. Samples for hormones were taken by venipuncture between 08:00 and 10:00 h after an overnight fast. Blood was collected in heparinised tubes which were analyzed by Medical Research Laboratories. Commercial kits were used for the analysis of the hormones. Inter- and intraessay coefficients of variation were below 10%. Cortisol (normal value (08:00–10:00 h): 220–650 nmol/l) was assessed with a chemiluminescence immunoassay (DPC, The Netherlands). Prolactin (normal value: males: $<15\,\mu g/l$, females: $<22\,\mu g/l$), free T4 (normal value: 10–20 pmol/l) and TSH (normal value: 0.4–4.0 mE/l) were assessed with a fluorescence immunoassay (Perkin Elmer, Germany). DHEA (normal value males: 10.6–29 ng/dl, females: 9.8–26.7 ng/dl) and DHEA-S (normal value males: 5.2–8.7 μmol/l, females: 2.1–8.8 μmol/l) were assessed with a radio immuno-assay (DPC, the Netherlands).

2.4. Psychotherapy

Details of the BEP used in this study have been published previously (Gersons et al., 2004; Lindauer et al., 2005a) and are reviewed here only briefly. BEP is a protocolized individual treatment for PTSD which consists of 16 weekly sessions of 45–60 min each. The course of BEP was administered as prescribed by the manual (Gersons et al., 2004). It incorporates several intervention techniques also used in the effective–cognitive behavioral treatment protocols, such as psychoeducation, imaginary exposure, writing assignments and cognitive restructuring, but also includes a focal psychodynamic approach, in particular, in the phase of 'giving meaning' to the event as well as by using a farewell ritual at the end of the treatment.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 12.0.1. Paired-sample *t*-tests were used to detect differences over time in the continuous outcome measures of the IES-R and the BDI. To determine whether treatment was effective in reducing PTSD and coexisting MDD, we used the Pearson χ^2 test. Pearson correlation coefficients were calculated to determine which background variables influence hormone levels. We performed separate analyses of variance (ANOVA) with repeated measures to determine the effect of time and the effect of a continuing PTSD diagnosis at the end of treatment (i.e. responder versus non-responder) on the formerly mentioned hormone levels. Natural log transformations were used to make the distributions of hormone levels approximately normal. In all analyses the transformed values were used. For each hormone, three separate analyses were done. First, an ANOVA was performed with time (before, after) as within subjects factor and PTSD diagnosis (no, yes) as between-subjects factor. To control for background variables (age, body mass index), variables were added to the model if they had a sufficiently large influence ($r > 0.30$) on the hormone level under analysis. Second, an ANOVA was performed to control for the degree of depressive symptoms. For this purpose, we added the BDI score before treatment and the degree of BDI score change (difference in BDI scores before and after treatment) as covariates to the first model. Third, we performed an ANOVA with the interaction terms of PTSD diagnosis with the BDI score before treatment and the degree of BDI score change added to the model of the second ANOVA. For all ANOVAs, we determined that the equality of variances assumption was not violated using Levene's test of equality of error variances. For each separate hormone, we calculated the effect size of response using Cohen's *d*. Cohen proposed that *d* values of 0.2, 0.5 and 0.8 should be considered small, medium and large, respectively. In all analyses, a *p*-value $<.05$ was considered statistically significant.

3. Results

3.1. Subjects

Twenty-one subjects with PTSD participated in the study, of which eight patients (38.1%) had comorbid major depression. The demographic variables are described in Table 1. The sample consisted of a majority of female subjects with Dutch nationality and with mixed traumatic events.

Table 1 Sample description ($N = 21$).

Background variable	Mean	SD
Age (years)	45.6	(7.9)
Body Mass Index	25.8	(4.0)
	N	%
Female sex	16	(76.2)
Marital status		
Single/divorced	13	(61.9)
Married/cohabiting	8	(38.1)
Nationality		
Dutch	10	(47.6)
Turkish	6	(28.6)
Suriname	4	(19.0)
Other	1	(4.8)
Education		
None/Low	7	(33.3)
Middle	8	(38.1)
High	6	(28.6)
Current trauma		
Sexual trauma	2	(9.5)
Accident	5	(23.8)
Loss of loved one	6	(28.6)
Other	8	(38.1)
Smoking	6	(28.6)
On psychotropic medication	8	(38.1)

3.2. Change in clinical measures

After treatment 15 out of 21 patients (71.4%) no longer fulfilled criteria for PTSD and were free of comorbid depression (5/8 = 62.5%; $\chi^2 = 5.688$, $p = .017$). All IES-R subscale scores as well as the total score decreased significantly from pre- to post-treatment, as did the BDI depression score (see Table 2).

3.3. Change in hormone levels

The average values and standard deviations of the untransformed hormone values and the effects of treatment on the hormone levels are shown in Tables 3 and 4. To examine the effects of successful treatment we looked at the interaction effect of time of measurement (pre, post) with the diagnosis of PTSD after treatment (responders versus non-responders). The treatment was considered successful if a patient no longer fulfilled the criteria for PTSD (i.e. responder).

3.3.1. Cortisol

When we did not include depressive symptoms in our analyses (model I) no statistically significant effects of treatment on any of the six hormones were revealed. However, differences between successful or unsuccessful treatment were shown when controlling for the degree of depressive symptoms (model II). The level of cortisol was influenced by responding to treatment, as well as by the depressive symptoms at the beginning of treatment and the degree of change in depressive symptoms after treatment.

The cortisol responses over time differed significantly between responders and non-responders. That is, in responders cortisol levels increased (pre: adj. mean-215.4 nmol/l, post: adj. mean = 347.0 nmol/l), while in those unsuccessfully treated, cortisol levels decreased (pre: adj. mean = 480.0 nmol/l; post: adj. mean = 217.7 nmol/l). Additional one-way ANOVAs on the estimated cortisol level values showed a statistically significant difference in cortisol level after treatment between responders and non-responders ($F = 118.20$, $p < 0.001$), but not for cortisol level before treatment ($F = 1.10$, $p = 0.307$).

3.3.2. DHEA

Statistical analyses for the remaining hormones did not reveal any significant effects; however, the probability values for the effect of continuing PTSD on prolactin ($p = 0.136$) and DHEA ($p = 0.151$) were suggestive of underlying effects. Since PTSD and depression are not completely unrelated constructs, we tried to separate the effects of PTSD and depressive symptoms by adding two additional three-way interaction terms of time, PTSD responder and depressive symptoms (model III). As in previous models, we did not find statistically significant effects for prolactin. Adding the three-way interaction terms resulted in a better fitting model for DHEA.

The DHEA response over time differed significantly between responders and non-responders. In responders DHEA levels increased (pre: adj. mean = 5.92 ng/dl; post: adj. mean = 7.42 ng/dl), while in those unsuccessfully treated DHEA levels decreased (pre: adj. mean = 7.99 ng/dl; post: adj. mean = 6.57 ng/dl). One-way ANOVAs on the estimated DHEA level values showed that the level of

Table 2 Clinical variables before and after treatment.

Clinical instrument	Before treatment		After treatment			
	Mean	(SD)	Mean	(SD)	*t*	*P*
IES-R						
Total (0–110)	69.5	(9.3)	49.5	(14.1)	6.610	<0.001
Re-experiencing (0–40)	26.6	(4.4)	18.6	(5.7)	6.392	<0.001
Avoidance (0–40)	22.3	(4.8)	16.4	(5.8)	5.014	<0.001
Hyperarousal (0–30)	20.5	(3.4)	14.6	(4.7)	5.673	<0.001
Beck Depression Inventory	22.30	(10.6)	15.6	(11.4)	3.290	0.004

Table 3 Untransformed mean hormone levels and standard deviations before and after treatment together with effect sizes (Cohen's *d*).

Hormone	Before		After		Effect size
	Mean	SD	Mean	SD	
Cortisol (nmol/l)	281.76	78.10	331.62	140.47	0.44
TSH (mE/l)	1.55	0.94	1.46	0.97	0.09
fT4 (pmol/l)	14.1	2.12	13.70	2.20	0.19
Prolactin (μg/l)	7.17	3.22	8.52	4.33	0.35
DHEA (ng/dl)	6.43	1.83	6.99	2.14	0.28
DHEA-S (μmol/l)	4.60	2.30	4.28	2.35	0.14

Table 4 Effect of time, response to treatment and depressive symptoms on six HPA- and HPT-axis hormone levels.

Model	Effect	Cortisol			TSH			fT4			Prolactin			DHEA			DHEA-S		
		F	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2
I	Time	0.09	.770	.01	0.11	.748	.15	2.45	.135	.12	1.71	.207	.08	2.90	.106	.19	2.90	.106	.14
	Time * PTSD	2.78	.112	.13	0.08	.786	.01	0.10	.752	.75	0.23	.634	.01	2.46	.134	.12	0.58	.458	.03
	PTSD	0.44	.514	.02	1.50	.236	.06	0.31	.588	.02	2.05	.169	.11	0.55	.468	.12	0.13	.725	.01
II	Time	4.05	.060	.19	2.75	.117	.15	1.87	.191	.10	0.37	.552	.02	1.16	.297	.07	2.37	.144	.13
	Time * PTSD	9.54	*.007*‡	.36	0.07	.799	.00	0.77	.393	.05	2.44	.136	.13	2.27	.151	.12	0.02	.878	.00
	Time * BDIpre	5.65	*.029*†	.25	0.00	.969	.00	0.28	.604	.02	1.58	.225	.09	0.70	.417	.04	0.09	.775	.01
	Time * BDIΔ	5.52	*.031*†	.25	0.03	.862	.00	1.53	.233	.09	2.96	.103	.15	0.62	.441	.04	0.01	.913	.00
	PTSD	0.35	.561	.02	0.00	.991	.00	0.01	.935	.00	0.00	.977	.01	0.05	.835	.00	0.20	.660	.01
III	Time	4.77	*.045*†	.24	2.02	.178	.13	1.30	.273	.09	1.07	.318	.07	0.08	.778	.01	0.99	.338	.07
	Time * PTSD	4.49	.051	.23	0.00	.968	.00	0.17	.689	.01	2.00	.177	.12	6.46	*.023*†	.32	0.38	.550	.03
	Time * BDIpre	5.44	*.034*†	.27	0.00	.958	.00	0.89	.362	.06	1.87	.191	.11	5.16	*.039*†	.27	0.17	.688	.01
	Time * BDIΔ	2.12	.166	.12	0.06	.818	.00	0.93	.351	.06	0.90	.357	.06	0.11	.748	.01	0.17	.685	.01
	Time * PTSD * BDIpre	0.35	.566	.02	0.05	.829	.00	0.14	.712	.01	0.31	.585	.02	0.59	.454	.04	0.23	.643	.03
	Time * PTSD * BDIΔ	0.16	.698	.01	0.03	.862	.00	0.94	.350	.06	0.16	.698	.01	5.21	*.039*†	.27	0.48	.499	.02
	PTSD	0.61	.446	.04	0.29	.597	.02	2.33	.150	.14	0.36	.559	.02	0.54	.477	.04	2.58	.131	.16

η^2: Partial squared η; Covariates added to the model to control for background variables: cortisol: no covariates; TSH: body mass index (r = 0.40); fT4: body mass index (r = −.32); Prolactin: no covariates; DHEA: age ($r = 0.38$); DHEA-S: age ($r = 0.45$).
†$p<0.05$.
‡$p<0.01$.

DHEA after treatment differed between responders and non-responders ($F = 6.17$, $p<0.022$). No differences were found for DHEA levels at the beginning of treatment ($F = 0.173$, $p = 0.682$).

4. Discussion

In this study we examined how psychological treatment for PTSD is associated with HPA-axis-related stress hormones in patients with PTSD. The main result is that effective psychotherapy may improve low cortisol and DHEA levels. These findings are in concordance with the single case report of Heber et al. (2002) who also found an increase in cortisol after psychological treatment for PTSD. Not only cortisol but DHEA also increased in responders to BEP. This may not be surprising since DHEA(S) are endogenous anti-glucocortoids involved in the feedback regulation of the HPA-axis. For the other hormones no statistically significant associations with psychotherapy were found. The effects on prolactin over time were not specifically related to improvement of PTSD symptoms. Similarly, although cross-sectional differences between PTSD and controls have been found for TSH (Olff et al., 2006a), no changes were detected in HPT-axis-related hormones after psychotherapy. This may be due to too little power or to a time frame too short after psychotherapy to result in changes in the thyroid system.

In cross-sectional studies lower basal cortisol levels have been found in PTSD patients, particularly when compared with healthy non-exposed controls (Olff et al., 2006b; Meewisse et al., in press). However, still very little is known about whether these levels were already pre-existent or arise due to the traumatic event and/or its consequences. Kellner et al. (2002) described in a single case report how cortisol levels may fluctuate and how improvement in PTSD is associated with potential renormalization of low cortisol levels. On the basis of a longitudinal study on cortisol levels in PTSD, Mason et al. (2001) suggest a psychogenic basis for fluctuations in cortisol alterations in PTSD. A small but interesting study by Aerni et al. (2004) shows that restoring the HPA-axis functioning by cortisol administration in PTSD patients gives a significant treatment effect, with cortisol-related reductions in cardinal PTSD symptoms.

Finding out whether neuroendocrine changes would be affected by psychotherapy may shed some light on the causal mechanisms of the dysregulations seen in PTSD. Although some patients may have a predisposition towards dysregulation of the endocrine system after trauma, the biological alterations in PTSD may be—at least in part—reversible by psychotherapy. No previous studies have examined—in more than a single case—whether, and to what extent, the neuroendocrine changes observed in PTSD are modified during the course of this illness, particularly as symptoms improve. It is of interest that biological changes in this study were associated with symptom improvement following a non-pharmacological intervention. The finding that neuroendocrine dysregulation can change over time in trauma survivors suggests that neuroendocrine markers may be useful in the assessment of treatment outcome in PTSD. Clearly, more research is needed in the area of therapeutic outcome and its biological correlates.

A mechanism through which psychotherapy may affect psychobiological responses to trauma may include cognitive appraisal and coping styles (Gersons et al., 2000; Bryant, 2003; Ehlers and Clark, 2003; Olff et al., 2005a). Cognitive appraisal, the subjective interpretation of the trauma, is crucial in starting the cascade of psychobiological responses to trauma. A failure to regulate the biological stress

response following trauma may result in a cascade of psychobiological alterations that lead to intrusive recollections of the event, avoidance of reminders of the event, and symptoms of hyperarousal (Olff et al., 2005a, b). Effective defensive coping may buffer the HPA acute stress response and may protect individuals from being overwhelmed (Olff et al., 2005a). Alternatively, generally active coping may help individuals deal with the traumatic stressor, avoiding long-term neuroendocrine dysregulation and post-trauma symptoms (for review, see Olff et al., 2005a), although in the acute aftermath of trauma when active coping is not always possible, this coping style may be associated with poor outcome (Malt, 1992; Schnyder et al., 2001; Hepp et al., 2005). Mason et al. (2001) suggest that their longitudinal cortisol findings fit with recent observations that cortisol elevations occur when acutely superimposed stressful conditions emotionally engage patients and overwhelm the usually dominating disengaging coping mechanisms associated with the suppression of cortisol levels in PTSD.

Interestingly, the effects of psychological treatment were only found when taking depressive symptoms and their improvement in the course of therapy into account. PTSD is often accompanied by comorbid disorders, depression in particular (Ackerman et al., 1998). Distinct biological alterations have been shown in PTSD and major depressive disorder (MDD) with respect to HPA-axis alterations. Ribeiro et al. (1993) found high cortisol levels in patients with MDD, and Young and Breslau (2004) in patients with comorbid PTSD–MDD. However, research examining PTSD patients, who also meet diagnostic criteria for MDD, show disparate results also with normal (Halbreich et al., 1989) and lower (Oquendo et al., 2003; Yehuda et al., 2004) cortisol levels. Also, for DHEA(S) both lower and higher levels were found in depressed subjects (Assies et al., 2004). In our study it became clear that depressive symptoms may obscure the effects of psychotherapy on cortisol, possibly because of opposite mechanisms of action.

Even though this is the first study to examine the effect of psychotherapy on HPA-axis hormones in more than '$n = 1$', limitations of the present study include the relatively low sample size. It is possible that small effects were not detected due to low statistical power. Another limitation is that a pre–post design without a control group makes it difficult to interpret the results as reflecting treatment-induced changes. For instance, habituation to the blood sampling in the laboratory may have affected physiological responses. This study only assessed 08:00 h levels of cortisol, and not the diurnal pattern or responsivity of the system such as in a dexamethasone suppression test. However, 08:00 h samples have been reported to be indicative of basal cortisol levels. A further limitation included not having follow-up assessment to obtain information on the duration and stability of the observed changes in the neuroendocrine system.

Future research will need to validate the findings of this study on the effects of psychotherapy for PTSD, preferably in a randomized controlled design with larger sample sizes. Testing the responsivity of the neuroendocrine system by using challenge tests might provide more insight in the dynamics of the system. In our study the neuroendocrine profile was different for responders versus non-responders. Possibly, with more refined techniques treatment effects may be predicted from pre-treatment neuroendocrine profiles. Follow-up assessments are needed to investigate the neurobiological mechanisms that underlie long-term treatment effects and relapse. Lastly, further research should establish whether cortisol response to treatment is associated with gender and/or type of trauma (i.e. abuse) as has been shown for basal cortisol levels in PTSD (Meewisse et al., in press).

In conclusion, to our knowledge this is the first study in a sample of patients with PTSD to report increases in cortisol and DHEA after an intervention for PTSD, notably a non-pharmacological intervention. We hope this study stimulates further research in the area of psychological treatment for PTSD and its neurobiological correlates.

Role of the funding sources

The study was funded by the Academic Medical Center, Amsterdam, the Netherlands.

Conflict of interest

None.

Contributors

None.

Acknowledgments

We would like to thank the patients for participating in the research, and the reviewers for their helpful comments to the manuscript.

References

Ackerman, P.T., Newton, J.E., McPherson, W.B., Jones, J.G., Dykman, R.A., 1998. Prevalence of post traumatic stress disorder and other psychiatric diagnoses in three groups of abused children (sexual, physical, and both). Child Abuse Negl. 22, 759–774.

Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A., Nitsch, R.M., Schnyder, U., de Quervain, D.J., 2004. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am. J. Psychiatry 161, 1488–1490.

Altemus, M., Cloitre, M., Dhabhar, F.S., 2003. Enhanced cellular immune response in women with PTSD related to childhood abuse. Am.J. Psychiatry 160, 1705–1707.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, IV. American Psychiatric Association, Washington DC.

Assies, J., Visser, I., Nicolson, N.A., Eggelte, T.A., Wekking, E.M., Huyser, J., Lieverse, R., Schene, A.H., 2004. Elevated salivary dehydroepiandrosterone-sulfate but normal cortisol levels in medicated depressed patients: preliminary findings. Psychiatry Res. 128, 117–122.

Baker, D.G., West, S.A., Nicholson, W.E., Ekhator, N.N., Kasckow, J.W., Hill, K.K., Bruce, A.B., Orth, D.N., Geracioti, T.D., 1999. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am. J. Psychiatry 156, 585–588.

Beck, K.A.T., Beamesderfer, A., 1974. Assessment of depression: the depression inventory. Mod. Probl. Pharmacopsychiatry 7, 151–169.

Bradley, R., Greene, J., Russ, E., Dutra, L., Westen, D., 2005. A multidimensional meta-analysis of psychotherapy for PTSD. Am. J. Psychiatry 162, 214–227.

Bryant, R.A., 2003. , Early predictors of posttraumatic stress disorder. Biol. Psychiatry 53, 789–795.

Carlier, I.V., Lamberts, R.D., Van Uchelen, A.J., Gersons, B.P., 1998. Clinical utility of a brief diagnostic test for posttraumatic stress disorder. Psychosom. Med. 60, 42–47.

Creamer, M., Bell, R., Failla, S., 2003. Psychometric properties of the impact of event scale—revised. Behav. Res.Ther. 41, 1489–1496.

Davidson, J., Smith, R., Kudler, H., 1989. Validity and reliability of the DSM-III criteria for posttraumatic stress disorder. Experience with a structured interview. J. Nerv. Ment. Dis. 177, 336–341.

Ehlers, A., Clark, D., 2003. Early psychological interventions for adult survivors of trauma: a review. Biol. Psychiatry 53, 817–826.

Gersons, B.P., Olff, M., 2005. Coping with the aftermath of trauma. BMJ 330, 1038–1039.

Gersons, B.P., Carlier, I.V., Lamberts, R.D., van der Kolk, B.A., 2000. Randomized clinical trial of brief eclectic psychotherapy for police officers with posttraumatic stress disorder. J. Trauma Stress 13, 333–347.

Gersons, B.P., Carlier, I.V., Olff, M., 2004. Manual brief eclectic psychotherapy (BEP) for traumatic stress disorder. Center for Psychological Trauma (University of Amsterdam), Amsterdam.

Goenjian, A.K., Pynoos, R.S., Steinberg, A.M., Endres, D., Abraham, K., Geffner, M.E., Fairbanks, L.A., 2003. Hypothalamic–pituitary–adrenal activity among Armenian adolescents with PTSD symptoms. J. Trauma Stress 16, 319–323.

Halbreich, U., Olympia, J., Carson, S., Glogowski, J., Yeh, C.M., Axelrod, S., Desu, M.M., 1989. Hypothalamo–pituitary–adrenal activity in endogenously depressed post-traumatic stress disorder patients. Psychoneuroendocrinology 14, 365–370.

Heber, R., Kellner, M., Yehuda, R., 2002. Salivary cortisol levels and the cortisol response to dexamethasone before and after EMDR: a case report. J. Clin. Psychol. 58, 1521–1530.

Hepp, U., Moergeli, H., Buchi, S., Wittmann, L., Schnyder, U., 2005. Coping with serious accidental injury: a one-year follow-up study. Psychother. Psychosom. 74 (6), 379–386.

Kalimi, M., Shafagoj, Y., Loria, R., Padgett, D., Regelson, W., 1994. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). Mol. Cell. Biochem. 131, 99–104.

Kellner, M., Yehuda, R., Arlt, J., Wiedemann, K., 2002. Longitudinal course of salivary cortisol in post-traumatic stress disorder. Acta Psychiatr. Scand. 105, 153–155.

Lemieux, A.M., Coe, C.L., 1995. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom. Med. 57, 105–115.

Lindauer, R.J., Gersons, B.P., Van meijel, E.P., Blom, K., Carlier, I.V., Vrijlandt, I., Olff, M., 2005a. Effects of brief eclectic psychotherapy in patients with posttraumatic stress disorder: randomized clinical trial. J. Trauma Stress 18, 205–212.

Lindauer, R.J., Vlieger, E.J., Jalink, M., Olff, M., Carlier, I.V., Majoie, C.B., den Heeten, G.J., Gersons, B.P., 2005b. Effects of psychotherapy on hippocampal volume in out-patients with posttraumatic stress disorder: a MRI investigation. Psychol. Med. 35 (10), 1421–1431.

Lindauer, R.T., Van meijel, E.P., Jalink, M., Olff, M., Carlier, I.V., Gersons, B.P., 2006. Heart rate responsivity to script-driven imagery in posttraumatic stress disorder: specificity of response and effects of psychotherapy. Psychosom. Med. 68, 33–40.

Lindley, S.E., Carlson, E.B., Benoit, M., 2004. Basal and dexamethasone suppressed salivary cortisol concentrations in a community sample of patients with posttraumatic stress disorder. Biol. Psychiatry 55, 940–945.

Malt, U.F., 1992. Coping with accidental injury. Psychiatr. Med. 10, 135–147.

Mason, J.W., 1968. A review of psychoendocrine research on the pituitary–thyroid system. Psychosom. Med. 30 (Suppl-81).

Mason, J.W., Wang, S., Yehuda, R., Riney, S., Charney, D.S., Southwick, S.M., 2001. Psychogenic lowering of urinary cortisol levels linked to increased emotional numbing and a shame-depressive syndrome in combat-related posttraumatic stress disorder. Psychosom. Med. 63 (3), 387–401.

Meewisse, M.L., Reitsma, J.B., Vries de, G.J., Gersons, B.P.R., Olff, M. Cortisol and posttraumatic stress disorder in adults: a systematic review and meta-analysis. Br. J. Psychiatry, in press.

National Institute of Clinical Excellence, 2005. Posttraumatic stress disorder: the management of PTSD in adults and children in primary and secondary care. National Clinical Guideline, vol. 26. Report. No. 26. Gaskell, London.

Olff, M., Langeland, W., Gersons, B.P.R., 2005a. Effects of appraisal and coping on the neuroendocrine response to extreme stress. Neurosci. Biobehav. Rev. 29, 457–467.

Olff, M., Langeland, W., Gersons, B.P.R., 2005b. The psychobiology of PTSD: coping with trauma. Psychoneuroendocrinology 30, 974–982.

Olff, M., Güzelcan, Y., de Vries, G.J., Assies, J., Gersons, B.P.R., 2006a. HPA- and HPT-axis alterations in chronic posttraumatic stress disorder. Psychoneuroendocrinology 31, 1220–1230.

Olff, M., Meewisse, M.L., Kleber, R.J., van der Velden, P.G., Drogendijk, A.N., van Amsterdam, J.G., Opperhuizen, A., Gersons, B.P., 2006b. Tobacco usage interacts with postdisaster psychopathology on circadian salivary cortisol. Int. J. Psychophysiol. 59, 251–258.

Olff, M., Langeland, W., Draijer, N., Gersons, B.P.R., 2007. Gender differences in posttraumatic stress disorder. Psychol. Bull. 133, 183–204.

Oquendo, M.A., Echavarria, G., Galfalvy, H.C., Grunebaum, M.F., Burke, A., Barrera, A., Cooper, T.B., Malone, K.M., John Mann, J., 2003. Lower cortisol levels in depressed patients with comorbid post-traumatic stress disorder. Neuropsychopharmacology 28, 591–598.

Pitman, R.K., Orr, S.P., 1990. Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol. Psychiatry 27, 245–247.

Rasmusson, A.M., Lipschitz, D.S., Wang, S., Hu, S., Vojvoda, D., Bremner, J.D., Southwick, S.M., Charney, D.S., 2001. Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol. Psychiatry 50 (12), 965–977.

Rasmusson, A.M., Vythilingam, M., Morgan III, C.A., 2003. The neuroendocrinology of posttraumatic stress disorder: new directions. CNS Spectrosc. 8, 651–657.

Ribeiro, S.C., Tandon, R., Grunhaus, L., Greden, J.F., 1993. The DST as a predictor of outcome in depression: a meta-analysis. Am. J. Psychiatry 150, 1618–1629.

Rinne, T., de Kloet, E.R., Wouters, L., Goekoop, J.G., de Rijk, R.H., van den, B.W., 2003. Fluvoxamine reduces responsiveness of HPA axis in adult female BPD patients with a history of sustained childhood abuse. Neuropsychopharmacology 28, 126–132.

Rohleder, N., Joksimovic, L., Wolf, J.M., Kirschbaum, C., 2004. Hypocortisolism and increased glucocorticoid sensitivity of pro-inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. Biol. Psychiatry 55, 745–751.

Schnyder, U., Moergeli, H., Klaghofer, R., Buddeberg, C., 2001. Incidence and prediction of posttraumatic stress disorder symptoms in severely injured accident victims. Am. J. Psychiatry 158, 594–599.

Sondergaard, H.P., Hansson, L.O., Theorell, T., 2002. Elevated blood levels of dehydroepiandrosterone sulphate vary with symptom load in posttraumatic stress disorder: findings from a longitudinal study of refugees in Sweden. Psychother. Psychosom. 71, 298–303.

Spitzer, B., Gibbon, R.L., Janet, M., Janet, W., 1995. Structured Clinical Interview For DSM-IV Axis I Disorders—Patient Edition (SCID-I/P, version2.0). American Psychiatric Press, New York.

Spivak, B., Maayan, R., Kotler, M., Mester, R., Gil-Ad, I., Shtaif, B., et al., 2000. Elevated circulatory level of GABA(A)—antagonistic neurosteroids in patients with combat-related post-traumatic stress disorder. Psychol. Med. 30, 1227–1231.

Tucker, P., Beebe, K.L., Burgin, C., Wyatt, D.B., Parker, D.E., Masters, B.K., et al., 2004a. Paroxetine treatment of depression with posttraumatic stress disorder: effects on autonomic reactivity and cortisol secretion. J. Clin. Psychopharmacol. 24, 131–140.

Tucker, P., Ruwe, W.D., Masters, B., Parker, D.E., Hossain, A., Trautman, R.P., et al., 2004b. Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder. Biol. Psychiatry 56, 121–128.

Wang, S., Mason, J., 1999. Elevations of serum T3 levels and their association with symptoms in World War II veterans with combat-related posttraumatic stress disorder: replication of findings in Vietnam combat veterans. Psychosom. Med. 61, 131–138.

Yehuda, R., Kahana, B., Binder-Brynes, K., Southwick, S.M., Mason, J.W., Giller, E.L., 1995. Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. Am. J. Psychiatry 152, 982–986.

Yehuda, R., Halligan, S.L., Golier, J.A., Grossman, R., Bierer, L.M., 2004. Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder. Psychoneuroendocrinology 29, 389–404.

Young, E.A., Breslau, N., 2004. Cortisol and catecholamines in posttraumatic stress disorder. Arch. Gen. Psychiatry 61, 394–401.