Trauma exposure in relation to basal salivary cortisol and the hormone response to the dex/CRH test in male railway employees without lifetime psychopathology

Psychoneuroendocrinology 2010;35:878-86

Ellen R. Klaassens
Erik J. Giltay
Tineke van Veen
Gerthe Veen
Frans G. Zitman
Abstract

Background
Dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis is hypothesized to underlie stress-related psychiatric disorders such as posttraumatic stress disorder (PTSD). We aimed to explore whether trauma exposure is associated with alterations in HPA-axis functioning in the absence of lifetime psychiatric morbidity.

Method
We included 39 trauma-exposed healthy male subjects (mean age=47.0 years; SD=9.2) and 24 non-exposed healthy male controls (mean age=47.4 years; SD=14.5). All subjects were free of lifetime psychopathology. Basal salivary cortisol levels (on two consecutive days) as well as the cortisol and adrenocorticotropic hormone (ACTH) response to the combined dexamethasone/corticotropin-releasing hormone (Dex/CRH) challenge test were analyzed using general linear models (GLM) adjusted for body mass index, age and smoking status.

Results
A blunted salivary cortisol awakening response was found in the exposed group compared to the non-exposed group \((F(1,57)=5.46, p=.02)\). Consistent with these findings, salivary diurnal cortisol was lower in the trauma-exposed versus non-exposed group \((F(1,57)=4.04, p=.05)\). No differences, however, were found between both groups for plasma cortisol or ACTH responses to the Dex/CRH test.

Conclusion
Low basal cortisol levels were found in trauma-exposed men, suggesting that HPA-axis alterations in men are associated with trauma exposure during adulthood, also in the absence of psychopathology.
Introduction

In many studies, associations have been found between trauma-related psychiatric disorders, such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), and hypothalamic-pituitary-adrenal (HPA)-axis dysregulation (for reviews see 1;2). Although the majority of people who are exposed to traumatic events do not develop psychopathology 3;4, some studies have reported HPA-axis dysregulation in trauma-exposed subjects in the absence of psychopathology, suggesting that trauma exposure is linked with HPA-axis functioning rather than psychiatric morbidity 5-8.

The effects of trauma exposure during adulthood on HPA-axis functioning have not been studied extensively, in contrast to the effects of trauma exposure during childhood. Studies on the effects of childhood trauma have rather consistently shown lower cortisol levels in trauma-exposed subjects without current PTSD 9-11 or without lifetime PTSD or MDD 12 compared to healthy controls. For studies on the effect of trauma exposure during adulthood results are mixed 5;7;13-17. Only a few studies have directly compared a trauma-exposed group without psychopathology (trauma-exposed controls) versus a non-exposed control group on HPA-axis functioning. A lower salivary cortisol awakening response (CAR) was found in trauma-exposed controls compared with non-exposed controls 7, suggesting that trauma exposure is linked to a blunted HPA-axis 7. In line with this, the suppression of cortisol after dexamethasone (dexamethasone suppression test – DST) was found to be enhanced in trauma-exposed controls compared to non-exposed controls 7. In another study, lower pre-dex morning cortisol was again found in trauma-exposed controls compared with non-exposed controls. However, trauma-exposed controls did not show an altered DST compared to non-exposed controls 5. The results of these studies suggest that trauma exposure is linked to a blunted HPA-axis functioning. Other studies, however, reported no difference between trauma-exposed controls and non-exposed controls in basal salivary cortisol 13;14, urinary cortisol 15 or plasma cortisol 16 or in the salivary CAR 17.

In this study, we extended the scope of the previous studies in several ways. First, in order to elucidate the effect of trauma exposure on HPA-axis functioning, trauma-exposed and non-exposed individuals were studied. Second, since studies among recovered depressive patients have shown that patients who recovered from prior psychiatric disorders may still show subtle changes in HPA-axis functioning, due to so-called ‘scarring’ 18-20, we have eliminated the potential influence of a psychiatric history on HPA-axis functioning, by excluding those subjects with such a history. Third, most
studies that compared trauma-exposed and non-exposed healthy subjects, have focused on the effect of childhood trauma on HPA-axis functioning during adulthood. Early in life, the HPA-axis is still in development and trauma exposure may have different effects during childhood compared to adulthood. Therefore, in this study, we exclusively focused on the effect of trauma exposure during adulthood. We hypothesized that HPA-axis functioning is associated with trauma exposure during adulthood. We compared trauma-exposed male railway employees with non-exposed male controls on basal cortisol, as measured by collecting multiple salivary cortisol samples on two consecutive non-working days, and on the dexamethasone/corticotropin-releasing hormone test (Dex/CRH).

**Method**

**Subjects**
A large survey was sent out to 1086 traindrivers and trainconductors employed with the Dutch Railways, in order to recruit male subjects exposed to trauma. A 7-item self-report work-related trauma questionnaire, designed specifically for this study, was used as a screening tool. The questionnaire asked about the experience of possible traumatic events that are known to occur on a regular basis while working as a train driver or train conductor (i.e., being subjected to severe verbal aggression, physical aggression or sexual assault, being spat in the face, being threatened with a weapon, and being involved in person-under train accidents, suicides or any other severe work related accidents or near accidents). The questionnaire inquired whether any of these traumatic events had happened at all and if yes, how frequent they had occurred. We calculated a sum score by adding up these frequencies. Eligible for the trauma group were men with a sum score of 10 or higher.

Traindrivers and conductors in the Netherlands are potentially subjected to very stressful situations such as person-under-train accidents, suicides, and passenger aggression. Every year, approximately 180 person-under-train suicides take place and approximately 100 passengers get injured in accidents involving trains in the Netherlands. In addition, many railroad employees regularly experience passenger aggression, ranging from severe verbal aggression to assault with a weapon. The survey further consisted of a letter introducing the study, a questionnaire assessing current psychological distress and one question concerning psychiatric history. Non-exposed
healthy male controls were recruited by advertisements in a local newspaper. Exclusion criteria for both groups were a psychiatric history (i.e., any Axis-I disorder as assessed with the Mini International Neuropsychiatric Interview, M.I.N.I.) \(^{22}\), current psychological distress, clinically significant adrenocortical and thyroid diseases, use of (herbal) medication affecting neuroendocrine functioning, any serious unstable medical condition, and working in nightshifts. For the control group, an additional exclusion criterion was any exposure to potentially traumatic events. The response rate to the survey was 70% (n=759). One hundred and thirty-one men were eligible for inclusion in the trauma-exposed group, 43 (33%) of which consented in participating. Reasons for declining participation were, among others, location being too far away, too time consuming, no spare days. Three subjects prematurely withdrew, resulting in a trauma-exposed group of 40 male subjects (median trauma score=19.5, IQR=15.0-26.8). Thirty-five individuals responded to our advertisement asking for healthy male subjects with no lifetime psychiatric history and no exposure to potentially traumatic events. Twenty-five non-exposed healthy male controls met all criteria and were included in the study. Written informed consent was obtained from all participants after a complete written and verbal description of the study. All participants received a financial compensation. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC), the Netherlands.

**Instruments**

The 7-item self-report work-related trauma questionnaire mentioned above was also used to calculate an incident score, i.e., the number of traumas that occurred at least once. We used this score for the statistical analyses as this rather conservative trauma measure is more valid than a sum score of the frequencies of all traumas \(^{23}\). The non-trauma-exposed control group was screened for trauma exposure with a trauma questionnaire similar to the one used for the trauma-exposed railway employees. However, instead of focussing on specific work related trauma exposure, we focussed on aggression, violence, threat, and severe accidents, in general. We feel, therefore, that the type of trauma exposure we addressed was comparable to that of the railway employees. Because of the influence of sustained childhood trauma exposure on HPA-axis functioning, childhood trauma was assessed using the Dutch version of the Early Trauma Inventory \(^{24};^{25}\), a structured interview with valid psychometric properties, designed to assess traumatic experiences before the age of 18.

Lifetime psychopathology was excluded with the M.I.N.I. Plus 5.0.0.-R, a
structured diagnostic interview developed to assess the presence of Axis-I disorders according to the DSM-IV diagnostic criteria, for which a Dutch translation was used \cite{22,26}. Current levels of psychological distress were measured with the Dutch translation of the BSI, a well validated 53-item self-report clinical rating scale, designed to assess psychological distress in patients as well as individuals not suffering from current psychopathology \cite{27}. The total mean BSI score generates an overall measure of psychopathological symptom severity. Internal consistency of the BSI is very good (Cronbach’s $\alpha=.096$), and validity is sufficient \cite{27}. A cut-off score of 0.70 on the total BSI score is used as an indicator of psychopathology \cite{28}.

**Procedure**

Data collection for each participant took place during a single day at the LUMC and two consecutive non-working days at home. On the morning of the test day, a routine medical examination, including the measurement of height and weight to calculate the body mass index (BMI), was performed and demographic variables, trauma exposure, and psychological variables were assessed.

**Saliva sampling protocol**

Subjects collected saliva samples on two consecutive non-working days using Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Participants were free to wake up either spontaneous or with the use of an alarm clock, but no later than 08:00h. Saliva was collected immediately upon awakening and 30 min, 45 min and 60 min after awakening for the cortisol awakening response (CAR). For the diurnal decline, additional samples were taken at 11:00h, 15:00h, 19:00h and 23:00h. All participants were instructed to take the first sample while still in bed, and to refrain from eating, drinking, smoking and brushing their teeth during the first hour after awakening as well as 30 min prior to collection of the additional samples.

Samples were stored at 7°C and returned to the clinic within one week after collection. At the laboratory, saliva samples were stored at -20°C. Saliva cortisol levels were determined with a competitive electrochemiluminescence immunoassay ECLIA, using a Modular Analytics E170 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). The sample volume was 20 $\mu$L. The detection limit was 2.0 nmol/l and the intra- and inter assay variability coefficients were less than 10%.
**Dex/CRH protocol**

Subjects were pretreated orally with 1.5 mg dexamethasone at 23:00h on the evening before the test. At 13:00h, participants rested in semi-supine position on a bed. An intravenous cannula was placed in the antecubital fossa at 13:45h and kept open with a saline drip (50 ml/hr). Sampling for baseline plasma cortisol and ACTH took place at 15:00h. At 15:02h, 100 μgram of human CRH (Ferring BV, Hoofddorp, the Netherlands), reconstituted in 1 ml of 0.9% saline, was administered in the cannula over 30 seconds. Blood samples were drawn at 15:30h, 15:45h, 16:00h, 16:15h, 16:30h and 16:45h, for cortisol and ACTH assessment. Blood samples were collected in EDTA tubes, kept on ice and directly transported to the laboratory for cortisol and ACTH measurements. Plasma cortisol levels were determined with the cortisol assay described above. Plasma ACTH levels were determined with a solid-phase, two-site sequential chemiluminescence immunometric assay (Immulate 2500, DPC, Los Angeles, USA). The sample volume was 75 μL. The detection limit was 1.1 pmol/l and the intra- and inter assay variability was less than 10%. All samples were assayed after thawing at 4 °C.

**Statistical analyses**

Demographic, psychological and trauma variables were compared between the two groups using independent samples t-tests and χ² tests.

For basal salivary cortisol, per sampling point, physiologically unlikely high values (i.e., > 50 nmol/l) were excluded from further analyses (0.2% of the data, i.e., 2 out of 992 samples) 29. Excluded and missing samples (1.1% of the data, i.e., 11 out of 992 samples) were substituted with the values of the same time point from the other day. The mean cortisol concentrations for each time point over the two sampling days were calculated, then logarithmically transformed because of their positively skewed distribution, and subsequently used in the statistical analyses. The mean cortisol levels immediately after awakening are referred to as the awakening cortisol concentrations (T1). Using the trapezoidal method 30, three composite measures for salivary cortisol were calculated. As a measure of the total salivary cortisol output during the first hour after awakening, the cortisol awakening response with respect to ground (CAR) as well as with respect to increase (CARᵢ) were calculated. As a measure of the total salivary cortisol secreted over the rest of the day, the area under the curve with respect to ground for the diurnal decline was calculated (AUCdiurnal).

For plasma cortisol and ACTH levels obtained with the Dex/CRH test, the AUC’s with respect to ground were calculated from untransformed data.
Chapter 5

Because the resulting AUC’s of plasma cortisol and ACTH had positively skewed distributions, they were subsequently logarithmically transformed. We used analysis of variance (ANOVA) to analyze group differences in salivary and plasma cortisol and plasma ACTH levels. With General Linear Model (GLM) for repeated measures, we examined whether cortisol and ACTH levels within our two groups showed the expected changes over time (effect of ‘time’). Log-transformed plasma cortisol and ACTH measures (7 time points per subject: at 15:00h, 15:30h, 15:45h, 16:00h, 16:15h, 16:30h and 16:45h) were the within-subject factors (i.e., ‘time’), and ‘group’ the between-subject factor. We also examined whether the patterns of these curves differed between the two groups (time*group effect) and whether groups differed on total output of cortisol and ACTH (group effect). As age and smoking status have been shown to affect cortisol secretion, and some previous studies have shown that HPA-axis functioning is affected by obesity, with elevated cortisol secretion in obese adults, we adjusted for these potential confounders in multivariate models. Analyses were carried out using SPSS 16.0. All tests were two-tailed and $p$-values <0.05 were considered statistically significant.

**Results**

Subject characteristics are shown in Table 1. There were no differences between the trauma-exposed and the non-exposed groups for age, marital status and smoking status. Groups differed on BMI and years of education. The overall measure of psychopathological symptom severity (BSI) was low, values were below the cut-off score of 0.70, and were therefore considered being of limited clinical relevance. By definition, the exposed railway employees reported significantly more traumatic events than the non-exposed controls. Childhood trauma assessed by the Early Trauma Inventory did not differ statistically significant between the groups (data not shown).

**Basal saliva cortisol levels**

Two exposed subjects and one non-exposed control subject failed to return their salivettes. As a result, the analyses of the salivary cortisol samples comprise 38 subjects in the exposed group and 24 subjects in the non-exposed control group. Figure 2 shows the changes over time for salivary cortisol. Analysis with univariate ANOVA showed a significant difference between the trauma-exposed and the non-exposed control group with the trauma-
Exposed subjects showing a lower CAR (Table 2). Adjustment for BMI, age and smoking status did not change the results. The awakening cortisol levels (T1) and the AUCdiurnal did not differ significantly. After adjustment for BMI, age and smoking status, the results reached borderline significance ($p=.06$; Table 2). Analyses using the CAR, however, did not reveal a difference between the groups ($p=.92$ after adjustment, data not shown).

GLM repeated measures analysis showed a significant effect for time ($F(2.0,$ $118.7)=14.6$, $p<.001$) for cortisol after awakening as well as during the rest of the day ($F(2.8,$ $166.6)=39.6$, $p<.001$). No significant group*time interactions were found, neither for cortisol in the first hour after awakening ($F(2.0,$ $118.7)=0.91$, $p=.41$) nor for the AUCdiurnal ($F(2.8,$ $166.6)=1.47$, $p=.23$). We observed a significant group effect in salivary cortisol levels in the first hour after awakening ($F(1,60)=4.74$, $p=.03$) with lower cortisol levels in the exposed group on all 4 time points. Adjustment for BMI, age and smoking status did not weaken these results ($F(1,57)=5.46$, $p=.02$). The cortisol samples over the rest of the day (diurnal decline) were non-significantly lower in the trauma-exposed group ($F(1,60)=1.98$, $p=.16$). However, after adjustment for BMI, age and smoking status, the trauma-exposed group showed a significantly lower cortisol level than the non-exposed controls ($F(1,57)=4.04$, $p=.049$).

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<table>
<thead>
<tr>
<th>Trauma-exposed men (n=40)</th>
<th>Non-exposed controls (n=25)</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Age, mean (SD) - yr</td>
<td>47.0 (9.2)</td>
<td>t(36.31)=.127</td>
<td>.90</td>
</tr>
<tr>
<td>- Living together n (%)</td>
<td>36 (90)</td>
<td>$\chi^2(1) = 4.95$</td>
<td>.05</td>
</tr>
<tr>
<td>- Years of education, mean (SD) - yr</td>
<td>10 (2)</td>
<td>t(38.10)=.3.81</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>- BMI$^1$, mean (SD) - kg/m$^2$</td>
<td>27.5 (3.5)</td>
<td>t(60)=3.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>- Current smoker, n (%)</td>
<td>11 (28)</td>
<td>$\chi^2(1) = .47$</td>
<td>.57</td>
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<tr>
<td><strong>Mental health</strong></td>
<td></td>
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<tr>
<td>- BSI$^2$ total score, mean (SD)</td>
<td>0.08 (0.08)</td>
<td>t(32.11)=.2.56</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Trauma-exposure</strong></td>
<td></td>
<td></td>
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<tr>
<td>- incident score$^3$, mean (SD)</td>
<td>4 (1)</td>
<td>t(39)=19.2</td>
<td>.000</td>
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</tbody>
</table>

$^1$BMI = Body Mass Index; $^2$BSI = Brief Symptom Inventory; $^3$incident score is the number of different incidents reported (range 0-7)
Chapter 5

Plasma cortisol and ACTH during the Dex/CRH test

The Dex/CRH test failed in one of the 40 trauma-exposed railway employees due to the inability to extract plasma samples and in two subjects of the non-exposed control group. As a result, the analysis of the Dex/CRH challenge test comprised 39 trauma-exposed subjects and 23 non-exposed controls. Figure 3 shows the changes over time for plasma cortisol and ACTH for the exposed and the non-exposed control groups during the Dex/CRH test. Analysis with univariate ANOVA revealed no differences between the two groups in the AUC’s of cortisol and ACTH (Table 2).

Table 2. Comparisons of basal salivary cortisol outcome measures and plasma cortisol and ACTH response to the Dex/CRH test in mentally healthy men with and without exposure to trauma

<table>
<thead>
<tr>
<th></th>
<th>N (trauma / controls)</th>
<th>Trauma-exposed men</th>
<th>Non-exposed controls</th>
<th>Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal salivary cortisol:</strong></td>
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<tr>
<td>• awakening (T1) (nmol/l)</td>
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<tr>
<td>• Unadjusted mean</td>
<td>38 / 24</td>
<td>14.6 (13.2-16.1)</td>
<td>16.6 (14.7-18.8)</td>
<td>F(1,60)=2.66</td>
<td>.11</td>
</tr>
<tr>
<td>• Adjusted mean(^1)</td>
<td>38 / 24</td>
<td>14.4 (12.9-15.9)</td>
<td>17.1 (14.9-19.6)</td>
<td>F(1,57)=3.68</td>
<td>.06</td>
</tr>
<tr>
<td>• CAR(^2) (nmol/l/h)</td>
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<td></td>
<td></td>
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<tr>
<td>• Unadjusted mean</td>
<td>38 / 24</td>
<td>14.5 (13.2-16.0)</td>
<td>17.0 (15.1-19.2)</td>
<td>F(1,60)=4.23</td>
<td>.04</td>
</tr>
<tr>
<td>• Adjusted mean(^1)</td>
<td>38 / 24</td>
<td>14.3 (13.0-15.8)</td>
<td>17.3 (15.2-19.7)</td>
<td>F(1,57)=4.94</td>
<td>.03</td>
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<tr>
<td>• diurnal decline(^3) (nmol/l/h)</td>
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<tr>
<td>• Unadjusted mean</td>
<td>38 / 24</td>
<td>6.0 (5.2-6.8)</td>
<td>7.0 (5.9-8.3)</td>
<td>F(1,60)=2.25</td>
<td>.14</td>
</tr>
<tr>
<td>• Adjusted mean(^1)</td>
<td>38 / 24</td>
<td>5.9 (5.2-6.6)</td>
<td>7.1 (6.1-8.3)</td>
<td>F(1,57)=3.69</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Dexamethasone/corticotropin-releasing hormone (Dex/CRH) test:</strong></td>
<td></td>
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<tr>
<td>• AUC(_g) cortisol (nmol/l/h)</td>
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<tr>
<td>• Unadjusted mean</td>
<td>39 / 23</td>
<td>94.7 (69.3-129.5)</td>
<td>79.6 (53.0-119.7)</td>
<td>F(1,60)=0.46</td>
<td>.50</td>
</tr>
<tr>
<td>• Adjusted mean(^1)</td>
<td>39 / 23</td>
<td>101.5 (73.3-140.6)</td>
<td>70.8 (45.7-109.7)</td>
<td>F(1,57)=1.57</td>
<td>.22</td>
</tr>
<tr>
<td>• AUC(_g) ACTH (ng/l/h)</td>
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<td></td>
</tr>
<tr>
<td>• Unadjusted mean</td>
<td>39 / 23</td>
<td>13.2 (11.4-15.3)</td>
<td>15.4 (12.7-18.7)</td>
<td>F(1,60)=1.65</td>
<td>.21</td>
</tr>
<tr>
<td>• Adjusted mean(^1)</td>
<td>39 / 23</td>
<td>14.0 (12.1-16.2)</td>
<td>13.9 (11.4-17.0)</td>
<td>F(1,57)=0.01</td>
<td>.98</td>
</tr>
</tbody>
</table>

\(^1\) Means are adjusted for age, body mass index and smoking status. Geometric means are shown for unadjusted data, \(p\)-values by analysis of variance are analyzed on logtransformed values. The 95% confidence interval is given between brackets. \(^2\) CAR indicates the area under the curve with respect to ground (AUC\(_g\)) for the salivary cortisol awakening response, i.e., the first hour after awakening; \(^3\) diurnal decline indicates the AUC\(_g\) for the salivary cortisol output over the rest of the day.
GLM repeated measures analysis showed a significant effect of time for plasma cortisol and ACTH after CRH infusion ($F(2.6, 156.6)=51.1$, $p<.001$ and $F(2.2, 131.7)=42.8$, $p<.001$, respectively). No significant effect of the group*time interaction was found, neither for cortisol ($F(2.6, 156.6)=0.52$, $p=.65$) nor for ACTH ($F(2.2, 131.7)=0.553$, $p=.60$), and no group effect was found for cortisol and ACTH. Adjustment for BMI, age and smoking status did not alter these results (data not shown).

**Discussion**

The main finding of this study is that trauma exposure during adulthood is associated with a blunted $\text{CAR}_g$ compared to healthy male controls without trauma exposure. There was also some evidence of lower basal cortisol over the rest of the day in the trauma-exposed versus non-exposed group, at least in the most sensitive repeated measures ANOVA. These findings support our hypothesis that basal HPA-axis functioning is related to trauma exposure per se in adulthood, and not necessarily to – as is often assumed – concomitant psychiatric morbidity. Yet, no difference in the cortisol and ACTH response to Dex/CRH was found between our trauma-exposed and non-exposed individuals. This finding suggests that trauma exposure during adulthood...
does not affect HPA-axis reactivity to a biological stressor in mentally healthy male subjects. However, this null finding needs to be interpreted with caution, and needs to be confirmed in future, larger studies. To our knowledge, this is one of the first studies to investigate HPA-axis reactivity using the Dex/CRH test in adult-trauma-exposed subjects and non-exposed controls, who are all free of lifetime psychopathology.

Our finding of a blunted CAR of trauma-exposed healthy male subjects is consistent with a study that examined basal salivary cortisol and the cortisol suppression to dexamethasone among trauma-exposed veterans with and without PTSD and non-exposed civilian controls. Similar to our findings, this study reported a lower CAR in deployment-related trauma-exposed male peacekeeping veterans compared with non-exposed male civilian controls, thus also suggesting that a blunted CAR is associated with trauma and not specifically with PTSD.

Our study also supports previous findings of a meta-analysis on basal cortisol and PTSD. In this meta-analysis, studies on childhood trauma exposure and trauma exposure during adulthood among men as well as women, were included. In a subgroup analysis between trauma-exposed and non-exposed controls, lower cortisol levels were found in PTSD-patients compared with non-exposed controls but not with trauma-exposed controls. This also indirectly suggests that a difference in basal cortisol levels is related to trauma exposure rather than to psychiatric morbidity.

However, some other studies are not in line with our findings on basal salivary cortisol. One study among female victims of domestic violence with and without PTSD, as well as non-exposed controls, reported no difference in morning cortisol between the exposed and the non-exposed women. In this study, however, only one morning cortisol sample was assessed, which is generally considered inadequate to assess cortisol dynamics. Another study, examining the awakening cortisol response as well as a diurnal profile among trauma-exposed male and female subjects with and without PTSD, reported no difference in the CAR between trauma-exposed controls and non-exposed controls, suggesting that HPA-axis alterations are not related to trauma exposure. However, in this study, no subgroup analyses between male and female subjects were performed but adjustment for sex did not alter the results.

As far as HPA-axis reactivity is concerned, no previous studies used the Dex/CRH test to compare trauma-exposed and non-exposed subjects who were free of lifetime psychopathology. Many studies, however, have used the DST to examine the feedback inhibition of dexamethsone on the HPA-axis in patients with PTSD. Only some of these studies compared trauma-exposed
and non-exposed subjects, again with mixed results. No differences in cortisol suppression between trauma-exposed and non-exposed subjects were reported in some studies, while other studies found more suppression in trauma-exposed than in non-exposed subjects.

The findings of a blunted salivary cortisol response to awakening and lower diurnal salivary cortisol, as shown in the present study, suggest an important and interesting implication for the study of HPA-axis functioning in relation to trauma exposure. For one, it stresses the importance of the careful selection of control subjects in future studies and to take note of the potential association between trauma exposure and HPA-axis (dys)function in mentally healthy subjects.

There may be several explanations for our findings. First, recurrent trauma exposure during adulthood may have altered basal HPA-axis functioning in adult men, free of psychopathology. Second, our findings of lower basal cortisol in trauma-exposed subjects are consistent with the idea that these exposed, mentally healthy subjects may be less prone to the development of psychopathology in case of trauma exposure, and therefore, might be more resilient to stress. A recent study by Mikolajczak et al. showed that resilience moderates cortisol secretion in anticipation of a stressor (i.e., highly resilient individuals secreted less cortisol than less resilient ones). In individuals with low cortisol as a trait characteristic, more stress would be needed to dysregulate and overstimulate the HPA-system, rendering these individuals with a more robust HPA-axis. Low cortisol, therefore, does not necessarily coincide with psychiatric morbidity in these individuals. On the other hand, low cortisol levels may be a consequence of adrenal exhaustion during the stress response. Finally, it may be that the individuals with low cortisol are more at risk to develop a stress-related psychiatric disorder later in life, especially when trauma exposure continues. Only prospective cohort studies may provide data on which it can be decided which of these hypotheses are true. Our finding of a blunted CAR in trauma-exposed subjects, however, needs to be interpreted cautiously. The fact that we have included train drivers and conductors as a study group may have affected our findings. It may well be that people who choose this particular profession (in which among others they are more likely to be confronted with violence, aggression and/or suicides) have another psychological and biological make-up than the men they were compared with. Furthermore, the fact that some of the train drivers and conductors were working irregular shifts, may have influenced the results, even though saliva was sampled on non-working days. None of the men, however, were working nightshifts since this was an exclusion criterion.

Some limitations need to be discussed. First, selection bias may have
been introduced as 69 of the 131 eligible railway employees have declined participation. Most people gave pragmatic reasons for not wanting to participate, such as finding the research location too far away or not wanting to or being allowed to take a day off from work. A second limitation is the fact that all our analyses were done in men, so our findings cannot be generalized to women. A third limitation is the fact that the retrospective cross-sectional design of this study precludes causal inferences and may introduce recall bias for trauma exposure. A final limitation is the fact that we did not assess other forms of trauma exposure during adulthood. However, all trauma-exposed participants reported 10 or more traumatic events, which we considered as being sufficiently severe to study its effects on HPA-axis regulation. Additional traumas were hypothesized to have an effect on the HPA-axis of similar direction.

Our study also has several strengths. First, we solely included subjects free of current and lifetime psychopathology. Most studies on the influence of trauma on HPA-axis functioning did not exclude subjects who had recovered from psychopathology. Studies among recovered depressives have shown that HPA-axis functioning may not return to normal, resulting in so-called scarring 18-20. Second, we did not only study baseline HPA-axis functioning but also HPA-axis reactivity to a pharmacological stressor. Third, we had our subjects collect saliva samples on two consecutive non-working days to reduce day-to-day variation 38;39.

In conclusion, this study supports the idea that trauma exposure is associated with basal HPA-axis alterations, even in the absence of psychiatric morbidity. Our results demonstrate that exposure to traumatic events during adulthood is associated with a blunted CAR in Dutch male railway employees free of lifetime psychopathology.
References


