Saliva Cortisol in Posttraumatic Stress Disorder: A Community Epidemiologic Study

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Background: *Stress activates the hypothalamic–pituitary–adrenal (HPA) axis, so it was expected that posttraumatic stress disorder (PTSD) would be associated with activation of this axis; however, studies have found both increased and decreased cortisol in PTSD. To address this question, we collected saliva cortisol at home in a subsample of a longitudinal epidemiologic sample.*

Methods: *Six hundred eighty-four persons randomly selected from the total sample of 913 were requested to collect saliva samples upon awakening and in the early evening. Of these, 538 responded with samples, 516 of whom met inclusion criteria. These were 68 exposed to trauma with lifetime PTSD, 265 exposed to trauma with no PTSD, and 183 never exposed to trauma.*

Results: *In a comparison of these three groups, lifetime PTSD revealed elevated evening saliva cortisol compared with exposed/no PTSD. When lifetime comorbidity with major depressive disorder (MDD) was included in the analysis, only persons with comorbid PTSD and MDD showed this evening elevation in cortisol. Persons with PTSD alone (never MDD) showed normal saliva cortisol levels, as did subjects with lifetime MDD alone.*

Conclusions: *Neither exposure to trauma nor PTSD alone is associated with alterations in saliva cortisol; however, elevated cortisol is found in PTSD comorbid with lifetime MDD.*

Key Words: Trauma, HPA axis, major depression, comorbidity

Exposure to trauma would be expected to activate the hypothalamic–pituitary–adrenal (HPA) axis. Consistent with this expectation, a number of other studies, particularly those examining women with posttraumatic stress disorder (PTSD), have found evidence of HPA axis hyperactivity in PTSD, particularly after childhood abuse (Heim et al 2000; Lemieux and Coe 1995; Maes et al 1998; Pittman and Orr 1990; Rasmussen et al 2001); however, studies by Yehuda and others in male combat veterans and elderly Holocaust survivors with PTSD have demonstrated "hypocortisolism" and enhanced negative feedback to low-dose dexamethasone (Boscarino 1996; Yehuda 2002; Yehuda et al 1993, 1995). Furthermore, this low cortisol phenotype persisted even in the presence of major depression (Yehuda 2002; Yehuda et al 2002). A recent report by Young et al (2004) examined saliva cortisol in a community sample of low-socioeconomic-status women with high exposure rates to trauma in both childhood and adulthood and found normal saliva cortisol in women with current and lifetime PTSD and a nonsignificant suggestion of higher cortisol in women with comorbid lifetime PTSD and past-year major depression.

We previously reported on 24-hour urinary free cortisol (UFC) and catecholamine excretion, collected in a sleep research center, from a community sample and demonstrated no effect of exposure to trauma on UFC nor an effect of lifetime PTSD on UFC (Young and Breslau 2004); however, we did find a significant increase in UFC in women with lifetime comorbid major depression and PTSD.

In this report, we examine the HPA axis function in a larger subset of this community sample, using morning and early evening saliva cortisol, collected in the home for 516 persons. Saliva cortisol collection is easier to obtain than urinary samples, and, more importantly, it is less prone to the stress of novelty on HPA axis assessment in the laboratory and demonstrates greater reliability than UFC for collection in the home environment.

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Methods and Materials

Sample and Procedures

The neurobiological investigation of PTSD was nested in a large-scale, longitudinal community study of young adults. The study was described previously (Breslau et al 2000, 2003). In brief, a sample of 1200 persons was randomly selected from all 21 to 30-year-old members of a large health maintenance organization in southeastern Michigan. Personal interviews were conducted in 1989 with 84% of the sample ($n = 1007$). Follow-up interviews were conducted in 1992, 1994, and 1999–2001. In each wave, more than 90% follow-up completion was achieved. In the 10-year follow-up in 1999–2001, 913 of the initial sample (91.1%) completed interviews. All subjects gave informed consent to participate in the biologic measures, and procedures were approved by the Henry Ford Hospital institutional review board. Biologic measures were collected for a subset of these respondents. From the sample of 913, we excluded subjects who had moved out of the area. A random sample of the remainder were asked to participate in the home saliva collection procedure ($n = 684$). Of these, 538 returned the saliva samples. Subjects with any medical illness requiring steroid administration and persons using opiate-containing medications were excluded from analysis. A total of 516 subjects provided valid saliva cortisol data for the current analyses (75.4% of those recruited). Table 1 presents the characteristics of the entire sample and the subset of the sample analyzed here. As can be seen, differences between the total sample and the subset with saliva cortisol were small. Subjects who were taking psychotropic medications (including antipsychotics, benzodiazepine, anticonvulsants, and antidepressants) were not excluded.

Saliva cortisol was collected with Salivettes (Sarstedt, Newton, North Carolina). Subjects were instructed in the use of the Salivettes by the interviewers, and written instructions demonstrating the use of the Salivettes were given to the subject. Subjects were asked to collect the morning sample within 30 min of awakening and before brushing their teeth. The evening sample was collected at approximately 7:00 PM, except we asked

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Table 1. Sample Characteristics: Gender, Race, Age, Lifetime Prevalence of Alcohol and Drug Use Disorders

	Biologic Sample (n = 516)	Total Sample (n = 913)
Gender (female)	67.8	62.69
Race (white)	83.5	81.05
Education		
<High school	3.1	3.5
High school	19.4	20.8
Part college	44.4	46.2
College	33.1	29.5
Alcohol A/D	32.0	32.09
Drug A/D	13.8	14.57
Age (y), mean (SD)	36.8 (2.1)	36.8 (2.2)

Values are %, except where noted. A/D, abuse/dependence.

that it be collected either before dinner or 2 hours after dinner. Sampling time, waking, bedtime, and mealtimes, as well as alcohol and nicotine use and any medication taken during the sampling day, were recorded by the subject. Samples and saliva logs were mailed in a postage-paid, padded mailer to Henry Ford Hospital and stored at −20°C until assay. On average, the subjects took the wake-up sample at 7:20 AM, 17 min after awakening. The evening sample was collected at 6:29 PM, 22 min before dinner.

Ascertaining PTSD

The National Institute of Mental Health–Diagnostic Interview Schedule (NIMH-DIS) (Robins et al 1989) for DSM-III-R was used to diagnose psychiatric disorders. The baseline interview in 1989 inquired about lifetime history of disorders, and each follow-up assessment inquired about disorders occurring during the interval period since the previous assessment. The diagnosis of PTSD in DSM-III-R requires exposure to a qualifying traumatic event and the presence of PTSD criterion symptoms that are linked to the traumatic event. Two earlier studies reported high concordance between the diagnosis of lifetime PTSD by lay interviewers using structured interviews based on the DIS and independent clinical re-interviews (Breslau et al 1998; Kessler et al 1995). The latter study used the Clinician-Administered PTSD Scale (Blake et al 1995; Weathers and Litz 1994) and reported a sensitivity of 76% and a specificity of 97% (Breslau et al 1998).

Hormone Assays

Salivary cortisol was assayed unextracted with DPC Coat-a-Count cortisol kits (DPC, Los Angeles, California) according to the manufactures directions for saliva cortisol. Interassay variability was 6.5%, intra-assay variation was 5%, and assay sensitivity was .1 ng/mL.

Statistical Analysis

All statistical analyses were performed on log-transformed data. Two series of analyses were conducted for cortisol. Significance was defined as $\alpha < .05$ for group differences and $\alpha < .1$ for interactions; significant differences were further examined with post hoc comparisons. Multiple regression analysis was used, with application of generalized estimating equations (GEE) (Diggle et al 1994; Liang and Zeger 1986; Zeger and Liang 1986), to test and estimate associations between group membership and cortisol across two time periods of the 24-hour diurnal cycle, AM and PM. The GEE approach permits simultaneous modeling of the relationship between group classification and hormone measures at the two time periods. Generalized estimating equations take into account correlations within persons over the multiple measures and use information on persons with incomplete data. The addition of interaction terms allowed us to examine whether differences across groups varied by time and by covariates (e.g., gender). When a significant interaction between time and group membership was detected, post hoc tests of differences by group membership across AM and PM were performed. The final model for the cortisol analysis is illustrated in the equation $Y = \alpha + \beta_1$ (group) + β_2 (time) + β_3 (group × time).

Table 2. Effect of Smoking Status on Saliva Cortisol

Current Smoker	AM Cortisol n	AM Cortisol Mean (SD)	PM Cortisol n	PM Cortisol Mean (SD)
Yes	105	.449 (.324)	101	.157 (.162)
No	406	.480 (.32)	397	.140 (.159)

Because of the small number of cases of current PTSD (n = 9), we used lifetime PTSD (n = 68) for all data analyses. The first series of analyses focused on PTSD and exposure and consisted of comparisons across three groups: 1) PTSD (n = 68; 14 male, 54 female); 2) exposed/no PTSD (n = 265; 94 male, 171 female); and 3) not exposed (n = 183; 58 male, 125 female). It thus provided two control groups to which PTSD could be compared, including a group of persons who were never exposed, according to the baseline interview and the three follow-up assessments. The second series examined PTSD comorbid with major depressive disorder (MDD) and consisted of comparisons across four groups defined by history of PTSD and MDD: 1) neither disorder (n = 329; 125 male, 204 female); 2) MDD only (n = 119; 28 male, 91 female); 3) PTSD only (n = 27; 6 male, 21 female); and 4) both disorders (n = 41; 8 male, 33 female). All persons in the MDD group had reported at least one exposure in their lifetime, either before or after MDD onset. We tested whether subjects with current MDD (i.e., with symptoms continuing in the preceding 12 months) differed from remitted subjects but found no significant differences in cortisol. We therefore use lifetime disorders to classify respondents into the four diagnostic groups (MDD, PTSD, neither, and both).

Results

Salivary cortisol collected at home was available for 516 subjects. The 516 subjects included 265 subjects exposed to trauma, 183 subjects not exposed to trauma, and 68 with current and past PTSD. As observed in the Methods section, there were no differences between the biologic subset and the entire sample (Table 1). We first examined whether smoking or psychotropic drugs were associated with differences in saliva cortisol. We found no significant difference in mean cortisol levels between smokers and nonsmokers [$F(1) = .18$, $p = .67$] and no significant difference between AM and PM values of smokers and nonsmokers (Table 2). Similarly, we found no effect of psychotropic drugs (n = 37) on cortisol [$F(1) = 0$, $p = .992$; group × time interaction $F(1) = .25$, $p = .62$]. Finally, there was no effect of oral contraceptives or hormone replacement (n = 39) on saliva cortisol [$F(1) = .99$, $p = .65$].

We next addressed the question of whether exposure to trauma or the development of PTSD after exposure is associated with level of saliva cortisol, with the comparison of three groups: not exposed, exposed/no PTSD and exposed/PTSD. We observed a significant group × time effect [$F(2,500) = 3.4$, $p = .033$, Table 3]. Post hoc tests revealed a significant difference in

Table 3. Effect of Exposure to Trauma on Saliva Cortisol

Group	*n*	AM Cortisol, Mean ± SD	PM Cortisol, Mean ± SD
No Exposure	183	.48 ± .3	.14 ± .15
Exposed/No PTSD	265	.48 ± .33	.14 ± .15
PTSD	68	.46 ± .32	.17 ± .18[a]

Data are shown as raw values, but analysis was performed on log-transformed data. Effects data: Time: $F(1,498) = 646.7$, $p < .0001$; Group: $F(2,508) = .45$, $p < .635$; Time × Group: $F(2,500) = 3.41$, $p < .0337$. PTSD, posttraumatic stress disorder.

[a] $p < .05$, PTSD vs. Exposed/No PTSD.

evening saliva cortisol between the exposed/no PTSD versus the PTSD group, with PTSD subjects demonstrating higher evening saliva cortisol than exposed/no PTSD subjects (Figure 1). The exposed/no PTSD group did not differ from the nonexposed group. Gender was included in the analysis, and no gender difference was observed in this pattern.

Our final analysis addressed the effect of psychiatric comorbidity. We contrasted four groups: neither PTSD nor MDD, PTSD only, MDD only, and both PTSD and MDD. The data are shown in Table 4. We found the expected effect of time on saliva cortisol [$F(1,494) = 349$, $p < .001$] and a significant group × time interaction [$F(3,497) = 2.44$, $p = .06$]. Post hoc comparisons found no significant effect of lifetime "pure" PTSD (i.e., PTSD only) on saliva cortisol. Likewise, there was no significant effect of lifetime pure MDD (i.e., MDD only) on saliva cortisol, although 35 individuals in the MDD group were currently taking antidepressant medications; however, there was a significant difference between the neither group and the comorbid group on evening cortisol, with the comorbid group demonstrating elevated saliva cortisol (Figure 2). This difference applied to both genders.

Discussion

These data, which demonstrate an effect of PTSD, particularly comorbid PTSD and MDD, on cortisol, confirm and extend our previous findings on comorbid PTSD and MDD, using UFC (Young and Breslau 2004). In both studies, we observed an increase in cortisol in subjects with lifetime PTSD comorbid with lifetime MDD. In the study of UFC, this effect was seen across the circadian rhythm and in women only, although the number of male subjects was extremely small. In the current study, the

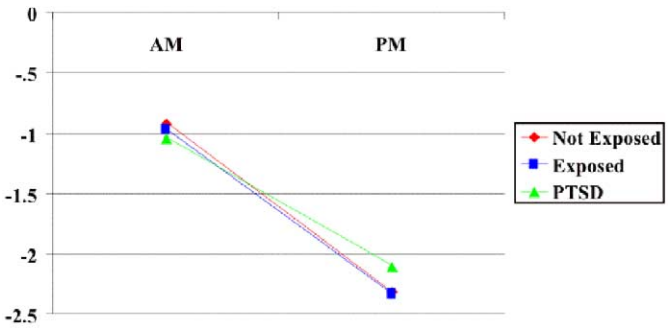

Figure 1. Morning (AM) and evening (PM) saliva cortisol levels in persons who were exposed to trauma with and without the development of posttraumatic stress disorder (PTSD) and the nonexposed group. Data are presented on a log scale. There was a significant group × time effect. Post hoc testing demonstrated that the PTSD group had a significantly increased evening cortisol compared with the exposed/no PTSD group.

Table 4. Saliva Cortisol by Diagnostic Group

Group	*n*	AM Cortisol, Mean ± SD	PM Cortisol, Mean ± SD
No MDD/No PTSD	329	.47 ± .32	.14 ± .16
MDD/No PTSD	119	.49 ± .33	.14 ± .16
No MDD/PTSD	27	.40 ± .15	.15 ± .13
MDD/PTSD	41	.50 ± .37	.19 ± .21[a]

Data are shown as raw values, but analyses were performed on log-transformed data. Effects data: Time: $F(1,494) = 349.15$, $p < .0001$; Group: $F(3,504) = .34$, $p < .79$; Group × Time: $F(3,497) = 2.44$, $p < .06$. MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

[a] $p < .0313$, MDD/PTSD vs. No MDD/No PTSD.

evening elevation in cortisol in comorbid PTSD and MDD was observed in subjects of both genders. This pattern of results observed in both saliva cortisol and UFC in this study of the general community is clearly different from the results reported by Yehuda et al (2002) for male combat veterans. It is, however, consistent with the results reported previously on women with a history of childhood abuse with current PTSD or MDD. Elevated basal activity based on 24-hour UFC was found in women with a history of childhood abuse and active PTSD (Lemieux and Coe 1995). Elevated basal UFC has also been observed in combat veterans (Pittman and Orr 1990) and in men and women with PTSD (Maes et al 1998). Elevated adrenocorticotropic hormone (ACTH) and cortisol responses to corticotropin-releasing hormone infusion were found in women with current PTSD, all of whom had lifetime comorbidity with MDD (Rassmussen et al 2001). In women with childhood abuse and current MDD (11 of 13 with comorbid PTSD), Heim et al (2000) reported increased ACTH and cortisol response to a social stressor. Thus, previous findings show with some consistency a hyperactive HPA axis in women with PTSD comorbid with MDD, as observed in the current study in both men and women; however, our ability to make conclusive statements regarding men is limited by their small number.

This study had two important strengths. The first is the representativeness of the sample, and second is the naturalistic context of the collection of saliva measures. Previous studies have examined PTSD in samples of convenience recruited by advertising or from persons who sought treatment, whereby selection bias might affect the results. Furthermore, bringing individuals into a laboratory setting for testing can itself stimulate

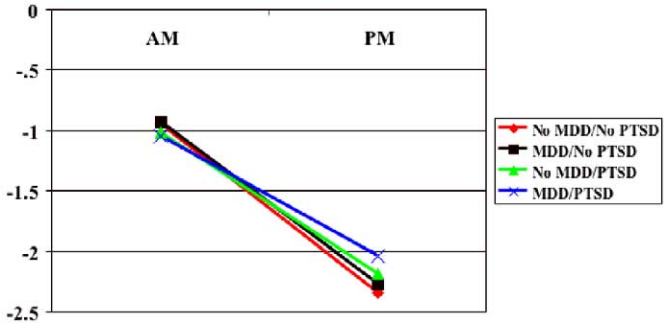

Figure 2. Morning (AM) and evening (PM) saliva cortisol levels in subjects with lifetime posttraumatic stress disorder (PTSD), major depressive disorder (MDD), both disorders (PTSD/MDD), or neither disorder. The data are shown on a log scale. There was a significant group × time interaction. Post hoc testing demonstrated that the group with both disorders had significantly increased evening saliva cortisol compared with the group with neither disorder.

the HPA axis, potentially obscuring subtle effects. Saliva sampling at home, as in this study, reduces the effects of novelty and captures the individual in their day-to-day home and work environment. Data from such sampling will be more likely to reflect the HPA axis activity in an everyday life situation. These data clearly demonstrate that lifetime PTSD, in the presence of comorbid lifetime depression, is associated with increased saliva cortisol, specifically in the evening, a pattern consistent with previous reports on plasma cortisol in patients with major depression (Halbreich et al 1985; Rubin et al 1987). The differences in the comorbid group were primarily from the "no disorder" (control) group. Our ability to discriminate between diagnostic groups is limited by sample size. This is especially true for PTSD/MDD versus PTSD only, because lifetime comorbidity is the rule. Also the other two diagnostic groups demonstrate changes in evening cortisol in the same direction as the comorbid group. We do not expect that MDD alone will necessarily differ from comorbid MDD/PTSD, because both groups would be expected to show elevated cortisol, and the degree of elevation is probably related to severity. Several studies have demonstrated that MDD comorbid with anxiety disorders is more severe than either alone (Clayton 1990; Coryell et al 1992; Brown et al 1996), so we would expect similar findings in the HPA axis. Although the effect seen in the evening might seem small, it is a 30% increase, which is similar to what has been reported for currently depressed patients with major depression, compared with normal control subjects (Young et al 2001). For the comparison of PTSD with the nonexposed, the post hoc comparison p value for PTSD versus not exposed was .07, whereas the post hoc comparison p value for PTSD versus exposed was .04, which is not very different; but because we used the p value standard of .05, we listed it as nonsignificant. Because persons who are not exposed have not been "tested" by exposure to trauma, the nonexposed group might include persons who have an underlying vulnerability to PTSD. We found significantly lower urinary catecholamines in the exposed group compared with the nonexposed group in subjects recruited from this sample (Young and Breslau 2004), which establishes some support for this hypothesis.

Limitations of this study include the use of lifetime versus current PTSD, less than 100% return of the saliva samples, only 1 day of saliva cortisol sampling, and the absence of a challenge test. In another study examining saliva cortisol in PTSD, we observed no difference between current PTSD ($n = 29$) and past PTSD ($n = 70$), which suggests that lifetime PTSD is a valid category (Young et al 2003). Furthermore, we were able to demonstrate elevated urine catecholamines in persons with lifetime PTSD, suggesting that differences associated with PTSD (related either to the persistence of biological abnormality or reflecting stable pre-existing characteristics) can be observed beyond the acute episodes (Young and Breslau 2004). In that same study (Young and Breslau 2004) and in another study examining saliva cortisol in women (Young et al 2000a) with a history of major depression, we were able to demonstrate increased cortisol in women with lifetime major depression, especially when comorbid with anxiety disorders, despite the absence of current symptoms. Regarding less than 100% return of saliva samples, we note that, although a 75% return rate is very high compared with other studies, the incomplete return limits the generalizability of the conclusions. The finding that the subgroup with data on saliva cortisol did not differ from the sample as a whole on diagnostic and socioeconomic status measures provides some reassurance that the subgroup we analyzed represents the sample as a whole on key variables. Nonetheless, we cannot rule out the possibility that there are differences on relevant but unmeasured variables.

Regarding the 1-day collection of saliva cortisol, the majority of studies on the HPA axis have examined only 1 day or a few hours of 1 day, so day-to-day variability is present in previous studies of the HPA axis in PTSD and depression. Regarding challenge tests, previous studies have demonstrated a strong relationship between baseline cortisol and postdexamethasone cortisol levels in both normal subjects in a large epidemiologic cohort that used low-dose dexamethasone (Huizenga et al 1998) and in subjects with major depression who used a higher dose of dexamethasone (Poland et al 1987). In studies in which enhanced negative feedback to cortisol have been found, basal levels of cortisol have also been low (Stein et al 1997; Yehuda et al 1992, 1993). Thus, our data on basal cortisol are inconsistent with a model of low cortisol and enhanced negative feedback in PTSD with comorbid lifetime depression. Most studies that examined depression in the absence of comorbid anxiety have found that use of activational challenges uncover additional HPA axis dysregulation beyond that seen with baseline cortisol or with dexamethasone, so we would expect this to be the case with comorbid PTSD and MDD (Young et al 1994, 2000b).

This study again finds persistent cortisol abnormalities in subjects with lifetime disorders (Bhagwagar et al 2003; Young et al 2000a, 2003), particularly lifetime major depression. This suggests that increased cortisol secretion is a trait rather than state phenomenon that could reflect pre-existing abnormalities rather than a consequence of prior depression. Furthermore, the increases in cortisol were found in the comorbid group only, which highlights the importance of comorbidities in examination of the HPA axis in psychiatric disorders and suggests that more attention should be paid to lifetime comorbidity in biological studies. Finally, further studies directly examining comorbid mood and anxiety syndromes are needed to understand the role of comorbid anxiety in determining the impact of stress and trauma on the HPA axis in major depression.

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