Published in final edited form as:

Psychol Trauma. 2014 September ; 6(5): 449–456. doi:10.1037/a0033013.

Awake/sleep cortisol levels and the development of posttraumatic stress disorder in injury patients with peritraumatic dissociation

Ihori Kobayashi and

Department of Psychology, Kent State University; Department of Psychiatry, Howard University

Douglas L. Delahanty

Department of Psychology, Kent State University, Department of Trauma Services, Summa Health System, Akron, Ohio

Abstract

Differences in the time of day that cortisol is sampled and failure to consider the impact of peritraumatic dissociation have been hypothesized as factors possibly contributing to the inconsistent findings in research examining associations between cortisol levels soon after trauma exposure and the subsequent development of posttraumatic stress disorder (PTSD). The present study examined associations between urinary cortisol levels during wake and sleep times soon after a serious injury and the subsequent development of PTSD in adult patients reporting low or high peritraumatic dissociative (PD) symptoms. Thirty-nine injury patients (20 with high and 19 with low PD symptoms) provided a 15-hour (6 PM to 9 AM) urine sample at 3-weeks post-injury and completed the Clinician Administered PTSD Scale at a 7-week follow-up. Participants collected their urine during wake and sleep times separately. Results showed that in the total sample and in the high PD group, wake, but not sleep, cortisol levels were lower in patients who developed PTSD compared to those who did not. A multiple linear regression analysis revealed a significant main effect of PD and a non-significant interaction between wake cortisol and PD in predicting PTSD symptom severity. In addition, results showed that PD was a better predictor of PTSD symptom severity than wake cortisol levels. These results were consistent with prior research indicating lower afternoon/evening cortisol levels in PTSD and strong associations between PD and PTSD, but did not support the existence of subgroups of PTSD patients (dissociators versus non-dissociators) who may differ in basal cortisol levels.

Keywords

urinary cortisol; PTSD; peritraumatic dissociation; Injury

Research examining associations between cortisol levels soon after exposure to a traumatic event and the risk for subsequently developing posttraumatic stress disorder (PTSD) has yielded mixed results (Bonne et al., 2003; Delahanty, Raimonde, & Spoonster, 2000; Shalev

et al., 2008). Failure to consider the presence of peritraumatic dissociation and time of day that cortisol was sampled have been hypothesized as factors possibly contributing to the inconsistent findings (Delahanty, Royer, Raimonde, & Spoonster, 2003; Griffin, Resick, & Mechanic, 1997; Meewisse, Reitsma, De Vries, Gersons, & Olf, 2007). However, research has yet to test the extent to which time of day and peritraumatic dissociation may impact the cortisol/PTSD link in the same study.

Research examining cortisol levels in patients with chronic PTSD has produced mixed results, with some studies finding higher 24-hour urinary cortisol levels in PTSD (Pitman & Orr, 1990) and some finding lower (Yehuda et al., 1990). A smaller number of studies have examined the extent to which cortisol levels assessed soon after a traumatic event are associated with subsequent PTSD symptoms, but these studies have also produced mixed results. Lower cortisol levels immediately after a motor vehicle accident were found in patients who subsequently developed PTSD compared to those who did not (Delahanty, Raimonde, & Spoonster, 2000) or those who developed depression (McFarlane, Atchison, & Yehuda, 1997). However, others did not find differences in urine, saliva, or plasma cortisol levels soon after a traumatic event between patients who later developed PTSD and those who did not (Bonne et al., 2003; Shalev et al., 2008).

The time of day that cortisol was sampled has been identified as a factor possibly contributing to the mixed results of studies examining cortisol levels in PTSD. A meta-analysis (Meewisse, Reitsma, De Vries, Gersons, & Olf, 2007) synthesizing results of 37 studies showed no overall differences in plasma/serum, saliva, or urinary cortisol levels between people with current PTSD and controls. However, subgroup analyses revealed lower cortisol levels in individuals with PTSD compared to controls in afternoon, but not morning plasma samples. These findings were consistent with results of studies not included in the meta-analysis (Bremner, Vermetten, & Kelley, 2007; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996) that measured plasma cortisol levels multiple times per hour throughout a 24-hour period and found significant differences between PTSD participants and controls only in afternoon/evening samples. In healthy adults, plasma cortisol levels peak immediately after morning awakening and decline during the wake period, especially during the last 4 hours of wake time, to reach nadir around evening sleep onset (Weitzman et al., 1971). Prior findings indicating lower afternoon/evening cortisol levels in people with PTSD may suggest that the afternoon/evening decline in cortisol is greater in people with PTSD. Although, as mentioned above, prospective studies have investigated cortisol levels immediately following trauma exposure in individuals who subsequently developed PTSD (Bonne et al., 2003; Delahanty, Raimonde, & Spoonster, 2000; Shalev et al., 2008), the time of day that cortisol was sampled was not taken into account in those studies.

Additional attempts to determine the impact of time of day of sampling have led to hypotheses that alterations in wake and sleep time stress hormone levels might be associated with increased PTSD risk. For instance, Mellman and colleagues' (Mellman, Kumar, Kulick-Bell, Kumar, & Nolan, 1995) study examining urinary 3-methoxy-4-hydroxyphenylglycol (MHPG, a metabolite of norepinephrine) levels found slightly increased MHPG levels from daytime (8 AM – midnight) to nighttime (midnight – 8 AM) in combat veterans with PTSD and decreased MHPG levels in non-combat veterans without PTSD. Further, this study

found an association between daytime-to-nighttime increases in MHPG levels and decreased total sleep time among participants with PTSD. As sleep disturbances soon after a traumatic event are related to increased risk for subsequently developing PTSD (Koren, Arnon, Lavie, & Klein, 2002; Mellman, David, Bustamante, Torres, & Fins, 2001; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002), it is possible that sleep time alterations in stress hormone levels soon after a trauma are also associated with the subsequent development of PTSD.

Another factor that has been proposed to account for inconsistent findings in the cortisol/PTSD literature is peritraumatic dissociation. Peritraumatic dissociative experiences include altered sense of time, place, and person accompanied by a sense of unreality (Marmar, Weiss, & Metzler, 1997). Meta-analytic studies have found positive relationships between peritraumatic dissociation and subsequent PTSD symptoms, and peritraumatic dissociation has been found to be the strongest predictor of PTSD symptoms relative to other pre- and peritraumatic risk factors (Lensvelt-Mulders et al., 2008; Ozer, Best, Lipsey, & Weiss, 2003). Griffin and colleagues (Griffin, Resick, & Mechanic, 1997) found that rape victims reporting high levels of peritraumatic dissociation exhibited attenuated autonomic nervous system responses while talking about their rape two weeks after their victimization. Similarly, trauma victims with high levels of peritraumatic dissociation were found to be less physiologically reactive to the index event than victims with lower levels of peritraumatic dissociation (Delahanty, Royer, Raimonde, & Spoonster, 2003). These findings suggest that there may be a subgroup of at-risk PTSD patients who report high levels of peritraumatic dissociation and who are physiologically less responsive to trauma-related stimuli. It has been further speculated that inclusion of this physiologically less responsive subgroup of trauma victims in prior studies might have obscured results examining physiological characteristics of PTSD patients (Griffin, Resick, & Mechanic, 1997).

As mentioned, research has indicated that differences in basal cortisol levels between individuals with and without PTSD tend to manifest during afternoon/evening times. These findings could be, in part, influenced by the presence of a subgroup of at-risk trauma victims with high peritraumatic dissociation who may have lower basal cortisol levels or may be less physiologically responsive. To explore this possibility, there is a need to prospectively examine the associations between time of cortisol sampling, peritraumatic dissociation, and risk of developing PTSD. Therefore, the aims of this study were to examine wake and sleep cortisol levels soon after trauma in recently injured patients with and without subsequent PTSD as well as to explore the role of peritraumatic dissociation in the association between post-trauma cortisol levels and the subsequent development of PTSD. Our hypotheses were as follows:

1. Time of cortisol assessment and PTSD status would interact to predict cortisol levels.
 - 1(a). We hypothesized that injury patients who subsequently developed PTSD would have lower wake time cortisol levels compared to those who did not develop PTSD, but the group difference would not be observed in sleep time cortisol levels.

1(b). In participants with subsequent PTSD, wake time cortisol levels would be lower than their sleep time cortisol, and in those without subsequent PTSD, wake cortisol levels would be higher relative to sleep time cortisol.

2. Peritraumatic dissociation would interact with cortisol levels to predict subsequent PTSD.

2 (a). In patients with high peritraumatic dissociation, lower cortisol levels would be associated with a greater risk of developing PTSD.

2 (b). In patients with low peritraumatic dissociation, cortisol levels would not be associated with subsequent PTSD status.

Method

Participants

Participants were 39 injury patients admitted to the level 1 trauma center of one of two Midwestern medical centers. To be eligible to participate, patients must have met the Diagnostic and Statistical Manuals of Mental Disorder-Fourth Edition (DSM-IV: American Psychiatric Association, 2000) Criterion A for PTSD (being exposed to a trauma and responding with intense fear, horror, or helplessness), must not have been amnesic for the event, and must not have been victims of potentially ongoing trauma (e.g., domestic violence). In addition, patients must have had a total score of the Peritraumatic Dissociative Experiences Questionnaire - Self-Report Version (PDEQ: Marmar, Weiss, & Metzler, 1997) of either 23 or less or 30 or higher. These cutoff scores were chosen because prior studies reported that trauma victims who subsequently developed PTSD scored, on average, 30 and 31 on the PDEQ, and victims who did not develop PTSD had a mean score of 23 (Birmes et al., 2001; Birmes et al., 2003). Twenty participants (13 males and 7 females) were categorized into the high PDEQ group and 19 participants (14 males and 5 females) were categorized into the low PDEQ group. A patient reporting being pregnant was excluded from analyses. Participant characteristics are presented in Table 1.

Procedure

The institutional review boards of Kent State University, Summa Health System, and Akron General Medical Center approved the following procedures. At Akron General Medical Center, participants were recruited during their hospital stay, and at Summa Health System, participants were recruited when they returned to the hospital for a follow-up clinic visit within two weeks after their injuries. None of the study or demographic variables except annual household income differed by recruitment site. Annual household income was marginally significantly different between the recruitment sites (Fisher's exact test: $p = .063$), with patients at Summa Health System reporting lower income. However, income was not associated with any study variables and was thus not controlled for in analyses. Potential participants were asked to complete the PDEQ as a screener; participants scoring as high or low peritraumatic dissociators on the PDEQ and whose injury event met DSM-IV criterion A were invited to participate. The research procedure was explained to potential participants, and if they were interested in participating, written informed consent was obtained. Eighty-five percent of patients meeting the inclusion criteria agreed to participate.

At 3-weeks post-injury, a researcher visited participants' homes to deliver two polypropylene urine containers and a cooler with ice for a 15-hour urine sampling starting at 6 PM on that day and ending at 9 AM on the following day. Following the procedures of Davidson and colleagues (Davidson, Fleming, & Baum, 1987), one of the urine containers was labeled "AWAKE" and the other was labeled "SLEEP." Participants were instructed to void all urine excreted from 6 PM until the time they went to bed that night into the awake container. All urine excreted from the time they went to bed through the first morning void was collected in the sleep container. All urine voided after the first morning void until 9 AM went into the awake container. Participants stored the containers in the cooler during the 15-hour urine sampling period. Sleep and wake samples did not differ in volume of urine collected [$t(38) = 1.05, p = .30$]. Urinary sampling was selected over salivary measures of cortisol as urine samples allow for measurement of average cortisol levels across the duration of the sampling period rather than a momentary measurement as provided by saliva samples. A saliva sample at awakening would only reflect cortisol secretion, at most, an hour prior to the sampling as the half-life of cortisol in saliva is approximately one hour (Nicolson, 2008). Further, the logistics of collecting sleeping salivary cortisol samples throughout the night without disrupting sleep led us to use urinary measures. A researcher picked up the urine samples in the afternoon on the day sampling was concluded. Participants also completed a questionnaire package including demographic information, a modified Traumatic Stress Schedule (Norris, 1990), self-reported height and weight, and a sleep diary that assessed the use of medication, caffeine, alcohol, tobacco, and recreational drugs during the day of urine sampling and sleep characteristics and nightmares on the night of urine collection.

At 7-weeks post-injury, participants were administered the Clinician Administered PTSD Scale (CAPS: Blake et al., 1995) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID: First, Spitzer, Gibbon, & Williams, 2002) in their homes to determine diagnostic status of PTSD and other psychiatric disorders. Participants' medical records were reviewed to obtain the Injury Severity Score (Baker, O'Neill, Haddon, & Long, 1974). Participants received \$10 for completing the initial assessment and \$30 for completing each follow-up assessment.

Measures

Urinary cortisol—Wake and sleep urine samples were aliquoted (60 ml) separately and frozen at -20°C . Urinary cortisol levels were measured using fluorescent polarization immunoassay (ARUP Laboratories, Salt Lake City, UT). Because cortisol levels were significantly correlated with urine volume in each sample [$r(37) = .51, p = .001$ for wake; $r(37) = .43, p = .006$ for sleep], analyses were conducted on cortisol levels per urine volume ($\mu\text{g/L}$).

Peritraumatic dissociation—The Peritraumatic Dissociative Experiences Questionnaire - Self-Report Version (PDEQ: Marmar, Weiss, & Metzler, 1997) is a 10-item questionnaire designed to measure retrospective reports of dissociative experiences during a traumatic event and immediately afterward. Respondents rated their dissociative experiences including derealization, depersonalization, disorientation, and altered time and body perception on 5-

point scales ranging from 1 (*Not at all true*) to 5 (*Extremely true*). The PDEQ was administered in an interview format and demonstrated high internal consistency ($\alpha = .90$).

PTSD and other psychological disorders—The Clinician Administered PTSD Scale (CAPS: Blake et al., 1995) is a structured interview designed to assess current and lifetime incidence of PTSD as well as the frequency and intensity of each of the 17 DSM-IV PTSD symptoms. The frequency and intensity of each symptom are rated on 5-point scales ranging from 0 [*Never* (frequency), *None* (intensity)] to 4 (*Daily or almost daily*, *Extreme*). A symptom was considered to be present when the frequency rating was 1 or greater and the intensity rating was 2 or greater (Blake et al., 1995). The CAPS has demonstrated good sensitivity (.84) and specificity (.95) against PTSD diagnosis assessed using the SCID (Blake et al., 1995), and in this study, internal consistency was high ($\alpha = .96$).

The SCID is a semi-structured diagnostic interview designed to assess a wide range of DSM-IV Axis I disorders (First et al., 2002). In the present study, the mood, anxiety, and substance use disorders modules were administered to assess current and lifetime diagnostic status of these disorders. The SCID has demonstrated moderate to superb inter-rater reliabilities ($\kappa = .75 - .85$) and a moderate 2-week test-retest reliability ($\kappa > .61$) for current diagnostic status (Rogers, 2001; Williams et al., 1992).

Trauma history—A modified Traumatic Stress Schedule (TSS: Norris, 1990) was used to assess participants' trauma history. Participants were instructed to report the lifetime frequency of 10 types of traumatic events. The 10 types consisted of seven items from the original TSS [robbery, assault, rape, motor vehicle crash (MVC), death of a loved one, fire, and other natural or manmade disaster] and three additional items: witnessing someone seriously injured or killed, non-MVC accident, and one open-ended question inviting participants to report any other types of traumatic events experienced. A lifetime trauma load (i.e., the total number of different types of trauma experienced) was computed.

Nightmares and substance use—The Pittsburgh Sleep Diary (PghSD: Monk et al., 1994) is a self-report questionnaire consisting of two sections, bedtime and wake time sections. The bedtime section includes questions about exercise, caffeine, alcohol, nicotine, and medication intake during the day. The wake time section assesses sleep timing, nighttime awakening, and sleep quality. In addition, participants were asked to report the number of nightmares (defined as very disturbing dreams) they had during the night. Participants completed the PghSD on the night of urine sampling and the following morning.

Injury severity—The Injury Severity Score (ISS: Baker, O'Neill, Haddon, & Long, 1974) was obtained from participants' medical records. The ISS is determined by squaring the sum of the injury severity rankings for the three most severely injured areas of the body and ranges from 0 to 75 with higher scores indicating more severe injury.

Analyses

Statistical analyses were conducted using SPSS version 20 (IBM, Armonk, NY). In all analyses, an alpha level of .05 was used. Participant characteristics were compared between

the PTSD and non-PTSD groups as well as between the high PDEQ and low PDEQ groups using *t*-tests for continuous variables and Fisher's exact tests for categorical variables. To examine the interaction between PTSD status and time of urine sampling, 2 (PTSD status) $\times$ 2 (Timing of sampling, wake vs. sleep) mixed-design ANCOVAs with timing of sampling as a repeated measure were performed with all participants and also with only participants with high PDEQ scores. We were unable to perform a 2 (PTSD status) $\times$ 2 (high vs. low peritraumatic dissociation) $\times$ 2 (Timing of sampling) ANCOVA because, as expected, only two participants in the low dissociator cell developed PTSD. Covariates were identified through Pearson correlation coefficients (between two continuous variables) and point-biserial correlations (between a continuous and a dichotomous variable). Potential covariates included gender, injury severity, current depression, past PTSD, lifetime trauma load, presence of childhood trauma, the number of minutes in bed on the night of urine sampling, exercise during the day of urine sampling, and the use of caffeinated drinks, alcoholic drinks, and tobacco products during the day of urine sampling. When a significant interaction effect was found, we conducted simple effect tests to examine differences between PTSD status groups in wake and sleep cortisol separately and differences between wake and sleep cortisol levels within each PTSD status group.

We also conducted a logistic regression analysis predicting 7-week PTSD status from 3-week wake cortisol levels, PDEQ group, and the interaction of wake cortisol $\times$ PDEQ group controlling for the use of cigarettes or other tobacco products, gender, past PTSD, and childhood trauma. A separate logistic regression with sleep cortisol levels, PDEQ, and sleep cortisol $\times$ PDEQ group interaction as predictors was also performed. Finally, multiple regression analyses were performed to predict continuous 7-week CAPS total scores from the same predictors as the logistic regression analyses.

Results

Participant Characteristics

Tables 1 and 2 show participant characteristics by PTSD status and PDEQ groups. Eleven (28%) participants met diagnostic criteria for PTSD at 7-weeks post-injury. Not surprisingly, results showed that the PTSD group reported higher peritraumatic dissociation ($d = 1.24$), current CAPS total scores ($d = 2.82$) and greater rates of past PTSD diagnoses ($\Phi = .45$) than the non-PTSD group (Tables 1 and 2). The high PDEQ group had higher peritraumatic dissociation ($d = 5.05$), current CAPS total scores ($d = 1.32$), and lifetime traumatic experiences ($d = 0.73$) than the low PDEQ group (Tables 1 and 2). Further, the PTSD group consisted of marginally more female participants ($\Phi = .32$) and individuals with childhood trauma exposure ($\Phi = .32$) than the non-PTSD group. The marginal findings are reported given concerns about Type 2 error due to the small sample size. No group differences were found in annual household income, education levels, and current and past psychopathology except past PTSD.

Sleep/Wake Cortisol Levels at 3-Weeks Post-Injury and Development of PTSD

Distributions of sleep and wake cortisol levels ($\mu\text{g/L}$) were examined for the PTSD and non-PTSD groups. Box plots indicated that the wake cortisol level of one PTSD participant (28.8

µg/L) was an outlier (2.7 SDs above the mean). This extreme value was replaced by a value that was 1 µg/L greater than the next highest value (12.2 µg/L) (Tabachnick & Fidell, 2000), which improved skewness and kurtosis values from 2.1 and 5.6 to -0.07 and -1.4, respectively. Cortisol levels for the PTSD and non-PTSD groups and high and low PDEQ groups within each PTSD condition are presented in Table 3. No participants reported taking medications that might affect cortisol levels.

Correlation coefficients between wake and sleep cortisol levels and possible covariates revealed a significant correlation between wake cortisol levels and the use of cigarettes or other tobacco products on the day of urine sampling ($r = .31, p = .05$). Given the greater proportion of women and individuals with past PTSD and childhood trauma in the PTSD group (Table 2), these variables were also included in the analysis as covariates along with the use of cigarettes or other tobacco products. Results of a 2 (PTSD status) $\times$ 2 (Timing of sampling) ANCOVA with timing of sampling as a repeated measure showed a significant main effect of timing of sampling [$F(1, 33) = 5.99, p = .020$, partial $\eta^2 = .15$] and a significant interaction effect [$F(1, 33) = 5.58, p = .024$, partial $\eta^2 = .15$] (Figure 1). The main effect of PTSD status was not significant [$F(1, 33) = 1.07, p = .308$, partial $\eta^2 = .03$]. Simple effects tests were conducted to examine the interaction effect. Results showed that the PTSD group had marginally lower wake cortisol levels compared to the non-PTSD group ($p = .059$), but the groups did not differ in sleep cortisol levels ($p = .735$) (Table 3). Results also revealed that the PTSD group had significantly lower wake cortisol levels compared to sleep cortisol levels ($p = .027$), but wake and sleep cortisol levels were not different in the non-PTSD group ($p = .279$) (Table 3).

The same ANCOVA was repeated with only high PDEQ participants. Results again revealed a significant PTSD status $\times$ Timing of sampling interaction [$F(1,14) = 5.34, p = .037$, partial $\eta^2 = .28$]. Neither the main effect of PTSD status [$F(1,14) = 3.10, p = .100$, partial $\eta^2 = .18$] nor the main effect of timing [$F(1,14) = 2.10, p = .170$, partial $\eta^2 = .13$] was significant. Simple effect tests revealed that the PTSD group had significantly lower wake cortisol levels compared to the non-PTSD group, but sleep cortisol levels were not significantly different between the groups ($p = .666$) (Table 3). Within the high PDEQ participants, wake and sleep cortisol levels were not significantly different in either the PTSD group ($p = .09$) or the non-PTSD group ($p = .073$) (Table 3). As mentioned, due to the low representation of low PDEQ participants with PTSD, an ANCOVA was not performed with low PDEQ participants.

No participants reported having nightmares similar to their index trauma on the night of urine sampling. Only four participants (2 high dissociators in the PTSD group, 1 high dissociator in the non-PTSD group, and 1 low dissociator in the non-PTSD group) reported having nightmares with content dissimilar to their index trauma on the night of urine sampling. The same ANCOVAs were performed without the four participants reporting nightmares, but results essentially did not change except that in the simple effect test, the PTSD group had significantly lower wake cortisol levels compared to the non-PTSD group [$F(1,29) = 4.18, p = .050$, partial $\eta^2 = .13$].

Effects of Cortisol x PDEQ Interaction on the Development of PTSD

To explore effects of the interaction between cortisol levels and PDEQ on the development of PTSD, we performed logistic regression analyses predicting PTSD status from wake or sleep cortisol levels, PDEQ group, and the cortisol x PDEQ interaction controlling for the use of cigarettes or other tobacco products, gender, past PTSD, and childhood trauma. When wake cortisol was one of the predictors, results revealed that the childhood trauma (0 = absent, 1 = present; $B = 3.39$, $p = .043$, OR = 29.57) and gender (0 = male, 1 = female; $B = 3.27$, $p = .043$, OR = 26.32) significantly predicted 7-week PTSD status; however, wake cortisol levels ($B = -1.42$, $p = .173$, OR = 0.24), PDEQ group (0 = low, 1 = high; $B = 1.81$, $p = .227$, OR = 6.12), or wake cortisol x PDEQ interaction ($B = -0.78$, $p = .447$, OR = .46) did not significantly predict PTSD status. When sleep cortisol was one of the predictors, results showed that the childhood trauma ($B = 3.84$, $p = .044$, OR = 46.48) and gender ($B = 3.94$, $p = .048$, OR = 51.36) significantly predicted 7-week PTSD status; however, sleep cortisol levels ($B = 0.05$, $p = .924$, OR = 1.06), PDEQ group ($B = 2.01$, $p = .129$, OR = 7.48), or sleep cortisol x PDEQ interaction ($B = -1.19$, $p = .149$, OR = 0.30) did not significantly predict PTSD status.

Multiple regression analyses were performed to predict continuous 7-week total CAPS scores with the same predictors as the logistic regression. When wake cortisol was one of the predictors, results indicated that childhood trauma ($\beta = .31$, $p = .006$), past PTSD ($\beta = .51$, $p < .001$), and PDEQ group ($\beta = .34$, $p = .003$) significantly predicted total CAPS scores, but wake cortisol levels ($\beta = -.002$, $p = .988$) or the wake cortisol x PDEQ interaction ($\beta = -.08$, $p = .497$) did not predict total CAPS scores. When sleep cortisol was one of the predictors, results indicated that childhood trauma ($\beta = .33$, $p = .003$), past PTSD ($\beta = .56$, $p < .001$), and PDEQ group ($\beta = .34$, $p = .003$) significantly predicted total CAPS scores, but sleep cortisol levels ($\beta = -.145$, $p = .169$) or sleep cortisol x PDEQ interaction ($\beta = -.09$, $p = .389$) did not predict total CAPS scores. Wake and sleep cortisol levels were not significantly correlated with high/low PDEQ groups ($r = .084$, $p = .609$, $r = -.033$, $p = .843$, respectively) or the presence of childhood trauma ($r = .01$, $p = .942$; $r = .08$, $p = .631$, respectively).

Discussion

The present study preliminarily examined prospective associations between 3-week post-injury wake/sleep urinary cortisol levels and the subsequent development of PTSD in injury patients as well as the role of peritraumatic dissociation in the associations. We first hypothesized that time of urinary sampling would interact with PTSD status to predict urinary cortisol levels. Overall, results were consistent with this hypothesis. Analyses with all participants indicated a significant PTSD status $\times$ Timing interaction. As hypothesized, cortisol levels in wake time urine [sampled from 6 PM to bedtime (Mean bedtime = 11:53 PM) and from the time of the first morning void until sample cessation at 9 AM] were marginally significantly lower in patients who subsequently developed PTSD than in patients who did not develop PTSD, but such group differences were not found in sleep cortisol levels. Limited statistical power due to the small sample size may have contributed to this marginally significant result, as the effect size was medium-large. We also

hypothesized lower wake time cortisol levels relative to sleep time in participants with subsequent PTSD and higher wake time cortisol levels relative to sleep time in participants without subsequent PTSD. Results partially supported this hypothesis. Wake cortisol levels were significantly lower than sleep cortisol levels in the PTSD group; however, wake and sleep cortisol levels were not different in the non-PTSD group. A significant PTSD status $\times$ Timing interaction was also found when the analysis was performed with only patients with high levels of peritraumatic dissociation; however, the interaction was not able to be tested in the low-PDEQ group due to the small number of low-PDEQ patients who developed PTSD ($n = 2$).

The reduced wake cortisol levels in the PTSD group may reflect simple lower basal HPA-axis afternoon functioning in PTSD or could reflect lower reactivity to various stimuli during wake time in PTSD participants compared to non-PTSD participants. Future research examining cortisol reactions to stimuli (both trauma-related and nontrauma-related) in both controlled lab environments and naturalistic settings using event sampling methods is necessary to explore factors contributing to the low wake cortisol levels in this group. Nightmares could serve as triggers for physiological reactions during sleep; however, only four participants (2 in each PTSD status group) reported having nightmares on the night of urine sampling. Multiple nights of nightmares and cortisol observations are needed to examine possible differential physiological reactivity to nightmares in individuals at greater and lower risk for developing PTSD.

We also examined whether peritraumatic dissociation interacted with wake or sleep cortisol levels to predict 7-week PTSD. No predictors (i.e., cortisol, PDEQ, or the interaction) predicted PTSD status; however, PDEQ predicted PTSD symptom severity beyond gender, childhood trauma, and past PTSD. These findings do not support our conceptualization of a subgroup of at-risk trauma victims with high peritraumatic dissociation and lower physiological responsiveness.

Extrapolating from the findings of the present study may lead to implications for studies examining the effectiveness of cortisol administration as a secondary intervention for PTSD (Schelling et al., 2001; Schelling et al., 2004). Increased cortisol levels after trauma have been hypothesized to potentially interrupt the development of PTSD through indirect and direct effects of cortisol on consolidation and retrieval of traumatic memory (Pitman & Delahanty, 2005). Given the lower wake cortisol levels sampled between 6 PM and bedtime in patients who developed PTSD in this study, cortisol intervention may be more beneficial during afternoon/evening time.

As peritraumatic dissociation predicted PTSD symptoms better than cortisol levels after accounting for covariates, the PDEQ could be used to identify individuals who are at risk for PTSD. Future studies should examine appropriate cut-off scores of the PDEQ to reliably identify trauma-exposed individuals at risk for PTSD.

This study suffers from several limitations. The small sample size did not allow us to conduct statistical analyses for the low peritraumatic dissociation group. However, given that high peritraumatic dissociation is a risk factor for PTSD, it would be difficult to recruit

high percentages of participants reporting low peritraumatic dissociation who meet PTSD criteria. The small sample size also limited statistical power, and a larger sample would be more adequately powered to address the aims of this study. Only a few potentially confounding factors were controlled for in the present analyses. Other factors associated with PDEQ and PTSD might have influenced cortisol levels, including lifetime trauma load and types of current trauma. In addition, urine sampling was not conducted over a complete 24-hour cycle. Although sampling over 24 hours would have allowed for complete wake and sleep levels of cortisol measurements, adherence to the urine sampling protocol can be a problem in 24-hour sampling especially during the workday, and leads to low adherence (Baum & Grunberg, 1995). Another limitation related to urine sampling is that wake urine samples included urine voided after the first morning void (when cortisol is at its highest) as well as afternoon/evening urine (when levels are at their lowest). However, given that morning sampling times only included urine voided after the first void and until 9 AM and afternoon sampling times lasted from 6 PM to bedtime, we consider that cortisol levels in the wake sample were mostly influenced by afternoon/evening urinary samples. Further, as the present study included only injury patients, the present findings may not generalize to victims of other types of traumatic events. Finally, the follow-up period was rather short (7 weeks); therefore, current findings are only applicable to acute PTSD and may not generalize to chronic PTSD patients.

Despite these limitations, the present study demonstrated that injury patients who subsequently developed PTSD had lower wake-time urinary cortisol levels at 3-weeks post-injury compared to those who did not develop PTSD. Such group differences were not observed in sleep-time cortisol levels. Lower afternoon/evening cortisol levels in chronic PTSD have been found in prior studies, and the present findings extend prior findings to recently traumatized individuals who are at risk for subsequently developing PTSD. Future studies with larger samples should extend the present study by systematically measuring physiological reactivity to various stimuli (e.g. trauma-related vs. non-trauma related) in individuals using both lab and naturalistic observation paradigms. The present study also replicated and extended prior findings regarding peritraumatic dissociation by indicating that PDEQ is a better predictor of subsequent PTSD symptom severity than cortisol levels. Future validation studies are needed to facilitate practical use of the PDEQ as a screener for PTSD development.

Acknowledgments

This research was supported by NIMH grants R34 MH71201 and R34 MH 73014 to Douglas Delahanty.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders - forth edition - text revision. Washington, DC: American Psychiatric Association; 2000.
- Andrews B, Brewin CR, Rose S, Kirk M. Predicting PTSD symptoms in victims of violent crime: The role of shame, anger, and childhood abuse. *Journal of Abnormal Psychology*. 2000; 109(1):69–73.10.1037/0021-843X.109.1.69 [PubMed: 10740937]
- Baker SP, O'Neill B, Haddon WJ, Long WB. The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *The Journal of Trauma*. 1974; 14(3): 187–196. [PubMed: 4814394]

- Baum, A.; Grunberg, N. Measurement of stress hormones. Oxford University Press; New York, NY, US: 1995.
- Birmes P, Brunet A, Carreras D, Ducasse JL, Charlet JP, Lauque D, Schmitt L. The predictive power of peritraumatic dissociation and acute stress symptoms for posttraumatic stress symptoms: A three-month prospective study. *The American Journal of Psychiatry*. 2003; 160(7):1337–1339.10.1176/appi.ajp.160.7.1337 [PubMed: 12832251]
- Birmes P, Carreras D, Ducasse JL, Charlet JP, Warner BA, Lauque D, Schmitt L. Peritraumatic dissociation, acute stress, and early posttraumatic stress disorder in victims of general crime. *Canadian Journal of Psychiatry Revue Canadienne De Psychiatrie*. 2001; 46(7):649–651.10.1097/00005053-200111000-00011 [PubMed: 11582828]
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS. The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*. 1995; 8(1):75–90.10.1002/jts.2490080106 [PubMed: 7712061]
- Bonne O, Brandes D, Segman R, Pitman RK, Yehuda R, Shalev AY. Prospective evaluation of plasma cortisol in recent trauma survivors with posttraumatic stress disorder. *Psychiatry Research*. 2003; 119(1-2):171–175.10.1016/S0165-1781(03)00098-2 [PubMed: 12860372]
- Bremner JD, Southwick SM, Johnson D, Yehuda R, Charney DS. Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. *American Journal of Psychiatry*. 1993; 150(2):235–239. [PubMed: 8422073]
- Bremner D, Vermetten E, Kelley ME. Cortisol, dehydroepiandrosterone, and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder. *Journal of Nervous and Mental Disease*. 2007; 195(11):919–927.10.1097/NMD.0b013e3181594ca0 [PubMed: 18000454]
- Breslau N, Chilcoat HD, Kessler RC, Davis GC. Previous exposure to trauma and PTSD effects of subsequent trauma: Results from the Detroit area survey of trauma. *American Journal of Psychiatry*. 1999; 156(6):902–907. [PubMed: 10360130]
- Davidson LM, Fleming R, Baum A. Chronic stress, catecholamines, and sleep disturbance at three mile island. *Journal of Human Stress*. 1987; 13(2):75–83.10.1080/0097840X.1987.9936798 [PubMed: 3611754]
- Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biological Psychiatry*. 2000; 48:940–947.10.1016/S0006-3223(00)00896-9 [PubMed: 11074232]
- Delahanty DL, Royer DK, Raimonde AJ, Spoonster E. Peritraumatic dissociation is inversely related to catecholamine levels in initial urine samples of motor vehicle accident victims. *Journal of Trauma & Dissociation*. 2003; 4(1):65–80.10.1300/J229v04n01_05
- DeViva JC, Zayfert C, Mellman TA. Factors associated with insomnia among civilians seeking treatment for PTSD: An exploratory study. *Behavioral Sleep Medicine*. 2004; 2(3):162–176.10.1207/s15402010bsm0203_5 [PubMed: 15600231]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. New York: Biometrics Research; 2002.
- Griffin MG, Resick PA, Mechanic MB. Objective assessment of peritraumatic dissociation: Psychophysiological indicators. *The American Journal of Psychiatry*. 1997; 154(8):1081–1088. [PubMed: 9247393]
- Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: A 1-year prospective study of injured survivors of motor vehicle accidents. *American Journal of Psychiatry*. 2002; 159(5):855–857.10.1176/appi.ajp.159.5.855 [PubMed: 11986142]
- Lensvelt-Mulders G, van der Hart O, van Ochten JM, van Son MJM, Steele K, Breeman L. Relations among peritraumatic dissociation and posttraumatic stress: A meta-analysis. *Clinical Psychology Review*. 2008; 28(7):1138–1151.10.1016/j.cpr.2008.03.006 [PubMed: 18502549]
- Marmar, CR.; Weiss, DS.; Metzler, TJ. The peritraumatic dissociative experiences questionnaire. In: Wilson, JP.; Keane, TM., editors. *Assessing psychological trauma and PTSD*. New York: Guilford; 1997. p. 412-428.

- McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. *Annals of the New York Academy of Sciences*. 1997; 821:437–441.10.1111/j.1749-6632.1997.tb48299.x [PubMed: 9238224]
- Meewisse M, Reitsma JB, De Vries G, Gersons BPR, Olff M. Cortisol and post-traumatic stress disorder in adults: Systematic review and meta-analysis. *The British Journal of Psychiatry*. 2007; 191(5):387–392.10.1192/bjp.bp.106.024877 [PubMed: 17978317]
- Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *American Journal of Psychiatry*. 2002; 159(10):1696–1701.10.1176/appi.ajp.159.10.1696 [PubMed: 12359675]
- Mellman TA, David D, Bustamante V, Torres J, Fins A. Dreams in the acute aftermath of trauma and their relationship to PTSD. *Journal of Traumatic Stress*. 2001; 14(1):241–247.10.1176/appi.ajp.159.10.1696
- Mellman T, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biological Psychiatry*. 1995; 38:174–179.10.1016/0006-3223(94)00238-X [PubMed: 7578660]
- Monk TH, Reynolds CF III, Kupfer DJ, Buysse DJ, Coble PA, Hayes AJ, Ritenour AM. The Pittsburgh sleep diary. *Journal of Sleep Research*. 1994; 3:111–120.10.1111/j.1365-2869.1994.tb00114.x
- Nicolson, NA. Measurement of cortisol. In: Luecken, LJ.; Gallo, LC., editors. *Handbook of physiological research methods in health psychology*. Los Angeles, CA: SAGE; 2008. p. 37-71.
- Norris FH. Screening for traumatic stress: A scale for use in the general population. *Journal of Applied Social Psychology*. 1990; 20(20):1704–1718.
- Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin*. 2003; 129(1):52–73.10.1037/0033-2909.129.1.52 [PubMed: 12555794]
- Pitman RK, Delahanty DL. Conceptually driven pharmacologic approaches to acute trauma. *CNS Spectrums*. 2005; 10(2):99–106. [PubMed: 15685120]
- Pitman RK, Orr SP. Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. *Biological Psychiatry*. 1990; 27(2):245–247.10.1016/0006-3223(90)90654-K [PubMed: 2294983]
- Rogers, R. *Handbook of diagnostic and structured interviewing*. New York: Guilford; 2001.
- Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhäusler H, Kapfhammer H. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biological Psychiatry*. 2001; 50:978–985.10.1016/S0006-3223(01)01270-7 [PubMed: 11750894]
- Schelling G, Kilger E, Roozendaal B, de Quervain DJ, Briegel J, Dagge A, Kapfhammer H. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: A randomized study. *Biological Psychiatry*. 2004; 55(6):627–633.10.1016/j.biopsych.2003.09.014 [PubMed: 15013832]
- Shalev AY, Videlock EJ, Peleg T, Segman R, Pitman RK, Yehuda R. Stress hormones and post-traumatic stress disorder in civilian trauma victims: A longitudinal study. part I: HPA axis responses. *International Journal of Neuropsychopharmacology*. 2008; 11(3):365–372.10.1017/S1461145707008127 [PubMed: 17971262]
- Tabachnick, BG.; Fidell, LS. *Using multivariate statistics*. 4th. Needham Heights, MA: Allyn & Bacon; 2000.
- Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *The Journal of Clinical Endocrinology and Metabolism*. 1971; 33(1):14–22.10.1210/jcem-33-1-14 [PubMed: 4326799]
- Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, Rounsaville B. The structured clinical interview for DSM-III–R (SCID): II. multisite test-retest reliability. *Archives of General Psychiatry*. 1992; 49(8):630–636.10.1001/archpsyc.1992.01820080038006 [PubMed: 1637253]
- Yehuda R, Southwick SM, Nussbaum G, Wahby VS, Giller EL, Mason JW. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *Journal of Nervous & Mental Disease*. 1990; 178(6):366–369.10.1097/00005053-199006000-00004 [PubMed: 2348190]

Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: A chronobiological analysis. *Biological Psychiatry*. 1996; 40:79–88.10.1016/0006-3223(95)00451-3 [PubMed: 8793040]

Figure 1.
Timing of sampling X PTSD status interaction.

Table 1

Participant Characteristics (Continuous Variables)

	PTSD (<i>n</i> = 11)		Non-PTSD (<i>n</i> = 28)		PDEQ high (<i>n</i> = 20)		PDEQ low (<i>n</i> = 19)		<i>t</i>
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	40.3	10.7	39.2	16.2	37.6	13.6	41.6	15.9	0.85
ISS	4.2	3.3	7.4	5.2	7.1	5.9	6.2	4.1	-0.54
BMI	26.2	6.0	28.5	7.4	27.0	7.4	28.8	6.7	0.76
Current CAPS total score	61.6	17.9	15.8	14.4	42.6	26.6	14.1	15.1	-4.13***
PDEQ	35.9	8.9	23.6	10.9	37.6	4.5	16.1	4.0	-15.81***
Lifetime trauma load ^a	3.9	2.1	3.1	1.9	4.0	2.1	2.6	1.7	-2.28*

Notes.

* $p < .05$,

** $p < .01$,

*** $p < .001$.

^a Lifetime trauma load is the total number of trauma type a participant experienced in lifetime. ISS = Injury severity score; BMI = Body mass index; CAPS = Clinician Administered PTSD scale; PDEQ = Peritraumatic dissociative experiences questionnaire.

Table 2

Participant Characteristics (Categorical Variables)

	PTSD (<i>n</i> = 11)		Non-PTSD (<i>n</i> = 28)		PDEQ high (<i>n</i> = 20)		PDEQ low (<i>n</i> = 19)	
	<i>n</i>	<i>p</i>	<i>n</i>	<i>p</i>	<i>n</i>	<i>p</i>	<i>n</i>	<i>p</i>
Race (White/Other)	7/4	.19	24/4	.19	6/14		2/17	.24
Gender (Female/Male)	6/5	.06 ⁺	6/22	.06 ⁺	7/13		5/14	.73
PDEQ (High/Low)	9/2	.03 [*]	11/17	.03 [*]	-		-	-
Trauma before age 18	10	.06 ⁺	16	.06 ⁺	15		11	.32
Past PTSD	5	.01 [*]	2	.01 [*]	6		1	.09
Types of trauma		.06 ⁺						.46
MVA/MCA	5		16		10		11	
Pedestrian	0		4		2		2	
Fall	2		5		4		3	
Non-sexual assault	3		0		3		0	
Other trauma	1		3		1		3	

Notes.

^{*} $p < .05$,

⁺ $p < .07$;

ps were computed using Fisher's exact tests. PTSD = Posttraumatic stress disorder; PDEQ = Peritraumatic dissociative experiences questionnaire; MVA = motor vehicle accident; MCA = motor cycle accident. Other trauma includes being hit by a falling object (PTSD group), work-related accident, gunshot wound, and falling from a tractor.

Table 3

Urinary Cortisol Levels

	All participants			PTSD			Non-PTSD			Partial η^2
	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	
Awake Cortisol ($\mu\text{g/L}$)										
All participants	16.1	16.5	11	7.7	3.8	28	19.3	18.4	3.82 ⁺	.104
High PDEQ	17.4	19.9	9	6.9	3.7	11	26.0	23.7	5.52 [*]	.283
Low PDEQ	14.6	12.3	2	11.4	1.1	17	15.0	13.0	<i>a</i>	--
Sleep Cortisol ($\mu\text{g/L}$)										
All participants	17.1	13.1	11	14.8	10.2	28	18.0	14.1	0.12	.004
High PDEQ	16.7	12.0	9	14.3	10.1	11	18.7	13.5	0.19	.014
Low PDEQ	17.6	14.4	2	17.1	14.4	17	17.6	14.9	<i>a</i>	
Wake vs. Sleep cortisol										
All participants			5.39 [*]		.140	1.21		Partial η^2	.035	
High PDEQ			3.32		.192	3.77			.212	

Notes.

 $p < .05,$
* $+ < .06.$

PDEO = Peritraumatic dissociative experiences questionnaire. Following ANCOVAs, simple effect tests were performed to examine differences between PTSD and non-PTSD groups (results are indicated in the *F* column) and between wake and sleep cortisol within each group (in the last two rows).

^a ANCOVA was not performed because only two participants in the low PDEQ group developed PTSD.