Research report

Hair cortisone level is associated with PTSD's dysphoric arousal symptoms in highly traumatized Chinese females

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1. Introduction

Exposure to traumatic stress is associated with increased risk for posttraumatic stress disorder (PTSD) and alterations of hypothalamic–pituitary–adrenocortical (HPA) function (Yehuda, 2009). Most of extant studies have found a hypoactive HPA axis in PTSD, as shown by lower cortisol levels in PTSD patients compared with control subjects and by inverse cortisol associations with PTSD symptom severity (Steudte et al., 2013). Circulating cortisol level is dynamically regulated partially through mutual transformation between cortisol and cortisone by enzymatic activity of 11β-hydroxysteroid dehydrogenase (Quinkler and Stewart, 2003). There is some evidence that cortisone is a useful additional biomarker for stress response (Gatti et al., 2005; Krumbholz et al., 2013; Vanaelst et al., 2013), and depressive disorders (Plenis et al., 2011; Römer et al., 2009). However, little is known about the status of cortisone alteration in PTSD. To date, there are two PTSD-related studies involved in cortisone assessment. Yehuda et al. (2009) reported that urinary total glucocorticoids (calculated as the sum of cortisol and its metabolites cortisone, 5α-tetrahydrocortisol, 5β-tetrahydrocortisol, and tetrahydrocortisone) were significantly negatively correlated with severity of avoidance symptoms in the tripartite phenotypic model of PTSD defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 2000), but uncorrelated with severity of total PTSD symptoms in survivors of the World Trade Center attacks at pre-treatment (N=28). Wheler et al. (2006) found that there were no demonstrable differences in cortisol levels in urine or serum between PTSD patients (n=10) and control individuals (n=10). However, these findings may be limited by small sample size.

Another particularly important factor concerns limitations in methods of cortisone assessment in previous studies. While PTSD is assumed to be associated with long-term changes in the activity of HPA axis, previous findings from serum, salivary or urinary samples only reflect short-term cortisol levels over periods ranging from minutes (e.g., saliva, plasma) to hours (urine) and could be affected by a host of potentially confounding factors such as the biological
phenotypic models of PTSD symptoms, emerging con- symptom clusters in reaction to traumatic stressors. Regarding the elucidating knowledge on long-term endocrine correlates of PTSD and traumatization. PTSD is a clinically heterogeneous mental disorder with distinct symptom clusters in reaction to traumatic stressors. Regarding the phenotypic models of PTSD symptoms, emerging confirmatory factor analytic studies demonstrate that a five-factor model comprised of intrusion (B1–B5), avoidance (C1–C2), emotional numbing (C3–C7), dysphoric arousal (D1–D3), and anxious arousal (D4–D5) is superior to the DSM-IV tripartite model and two variations of a four-factor solution (Elhai et al., 2011; Harpaz-Rotem et al., 2014; Pietrzak et al., 2014; Liu et al., 2014b). Some evidence indicates that distinct symptom clusters comprised of the five-factor model may be linked to different neurobiological correlates (Cao et al., 2013; Pietrzak et al., 2013a; Pietrzak et al., 2013b; Wang et al., 2013). Until now, to our knowledge, no study has examined how hair cortisone levels may relate to this newly proposed and empirically supported phenotypic model of PTSD symptomatology.

To further extend knowledge on long-term endocrine correlates of posttraumatic psychopathology, the current study determined physiological concentrations of cortisone in the hair of highly traumatized females, and investigated its relationship with severity of total PTSD symptoms as well as the five symptom dimensions of PTSD.

2. Methods and materials

2.1. Participants

The sample was recruited from a project aiming to provide psychological assistance for survivors who lost their children during the 2008 Wenchuan earthquake. Overall exclusion criteria included hair length <3 cm, presence of dyed hair, smoking, pregnancy, any severe physical disease such as cancer, and being treated with psychotropic or glucocorticoid-containing medications within the latest 3-month period. A total of 202 females participated in this study. One participant was excluded from the final analysis due to high outlying cortisone values of more than three standard deviations above the mean, leaving an effective sample of 201. All participants personally experienced the deadly earthquake in Beichuan County Town which was almost completely destroyed by the disaster. Detailed demographic characteristics of the sample are summarized in Table 1.

This study conducted four and a half years after the 2008 Wenchuan earthquake. The research protocol was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences, and all participants provided written informed consents.

2.2. Measures

The PTSD Checklist – Specific Stressor Version (PCL-S, Weathers et al., 1993) was used to measure PTSD symptoms. The PCL is a 17-item self-report scale that corresponds to the DSM-IV symptoms of PTSD. Using a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely), participants rate the severity of each PTSD symptom during the past month. As the most commonly used scale for assessing PTSD, the PCL has been shown to have excellent psychometric properties in a variety of populations (cf. McDonald and Calhoun, 2010; Wilkins et al., 2011). The Chinese version of the PCL was adapted by a rigorous two-stage process of translation and back translation. The reliability and validity of the Chinese version of the PCL has been well documented (cf. Li et al., 2010; Wang et al., 2011). In this sample, Cronbach’s α was .93 for the PCL. Symptoms were referent to the Wenchuan Earthquake in current study.

The Center for epidemiological studies depression scale (CES-D, Radloff, 1977) was used to measure depression symptoms. The CES-D is a self-reported scale, and consists of 20 items reflecting depressed mood, feelings of guilt or worthlessness, perceptions of helplessness or hopelessness, and psychomotor–somatic symptoms. Participants were instructed to indicate how often during the last week they experienced the symptoms, using a 4-point Likert scale ranging between 0 (rarely or none of the time) to 3 (most or all of the time). The CES-D has been validated and widely used in Chinese populations (e.g., Cheung and Bagley, 1998; Zhang et al., 2011). The Cronbach’s α for CES-D was .90 in this sample.

2.3. Hair cortisone analysis

Hair strands longer than 3 cm closest to the scalp in the participants’ vertex posterior region were collected. The hair sample was cut into 3 cm segment. The first 3 cm segment starting from the scalp to distal, was used for cortisone analysis. The details regarding the extraction of cortisone are available elsewhere (Qi et al., 2014). In this study, a 30 mg amount of the hair samples were used for 24-h incubation in methanol and 1 ml supernatant was utilized for solid phase extraction. The eluate finally obtained was evaporated to dryness and resuspended in 50 µl mobile phase for next detection. Detection was performed on liquid chromatography tandem mass spectrometer (LC–MS/MS) (3200Qtrap, ABI, USA). Cortisone was ionized with an atmospheric pressure chemical ionization source, and identified in positive ion mode using the multiple reaction-monitoring mode and quantified with internal standard method (Gao et al., 2013). The present LC–MS/MS method showed the limits of detection and quantification at .25 and .50 pg/mg. Recovery was 99.7 ± 8.7% (n=5) at 5 pg/mg, and intra-day and inter-day coefficients of variation were 6.5% (n=5) and 8.4% (n=3). As hair cortisone data were not normally distributed, the log-transformed data were used in analysis.

2.4. Data analysis

All statistical analyses were implemented using SPSS (Version19.0 for Windows). As an initial Shapiro–Wilk test indicated that the hair cortisone data were not normally distributed, the logarithmic-based-10 transformed data were used in further analysis. Group comparisons (i.e., probable PTSD group vs. non-PTSD group) regarding demographic and clinical characteristics, as well as hair cortisone levels, were conducted using one-way ANOVAs for continuous variables and χ² tests for categorical variables. An ANCOVA was further conducted to compare hair cortisone levels between the groups with age, marital status, education, and depression symptoms as covariates. Two simultaneous multivariate regression models were used to examine the relation between hair cortisone levels and the five-factor model of PTSD symptoms. It has been well documented that PTSD is a dimensional construct rather than a categorical one by previous taxometric studies (e.g., Bromlan-Fulks et al., 2006; Bromlan-Fulks et al., 2009; Forbes et al., 2005), suggesting that using the full range of symptom severity in analysis is appropriate and informative, and could also lead to higher statistical power and less bias in parameter estimation. Therefore, all participants rather than probable PTSD cases were included in the regression analyses.
the models, hair cortisone levels were set as the dependent variable, severity of total PTSD symptoms as well as its five symptom clusters were set as independent variables, and demographic variables (i.e., age, nationality, marital status, educational level) and clinical variable (i.e., severity of depression) were set as covariates.

3. Results

The mean score on PCL was 44.4 (SD = 13.7, range: 22–79) in this sample. According to the DSM-IV diagnostic algorithm of at least one intrusion symptom, three avoidance and emotional numbing symptoms, and two hyperarousal symptoms endorsed as 3 or greater, a total of 84 (41.8%) participants were identified as probable PTSD cases. Table 1 presents demographic and clinical characteristics of the non-PTSD and PTSD groups. The groups differed in term of age, marital status, educational level and depression severity, except for ethnicity. Compared to the non-PTSD group, the PTSD group reported greater severity of overall PTSD symptoms, as well as all symptom clusters.

In addition, an ANOVA showed that there were no significant differences between PTSD group (Mean = 2.14, SD = .38 log (pg/mg)) and non-PTSD group (Mean = 2.07, SD = .36 log (pg/mg)) regarding hair cortisone levels ($F(1, 199) = .78, p = .38, \eta^2 = .009$). A further ANCOVA, with age, marital status, educational level, and depression symptoms as covariates, also indicated that PTSD group did not significantly differ from non-PTSD group in term of hair cortisone levels ($F(1, 195) = .06, p = .803, \eta^2 = .000$).

The relation between hair cortisone levels and total PTSD symptoms was first examined. A simultaneous multivariate analysis indicated that there was no statistical significant association between hair cortisone levels and total PTSD severity after controlling for the potential effects of demographic variables (i.e., age, nationality, marital status, educational level) and clinical variable (i.e., severity of depression) (see Table 2). A subsequent analysis was further conducted to examine the relation between hair cortisone levels and five individual PTSD symptom clusters. Result showed that after controlling for the potential effects of covariates, hair cortisone levels only significantly associated with severity of dysphoric arousal symptoms, but not the other PTSD symptom clusters (see Table 3). Post-hoc analyses revealed that scores on the dysphoric arousal symptom D1 (i.e., sleep disturbance) was not significant ($\beta = .05$, $t = .48$, $p = .632$).

4. Discussion

By analyzing data yielded from a sample of highly traumatized Chinese females, this study examined the relation between hair cortisone levels and PTSD symptomatology. The result indicated that traumatized individuals with and without PTSD did not differ in term of hair cortisone levels, suggesting that hair cortisone may not be an ideal disease biomarker for PTSD. Further analyses revealed that hair cortisone levels were not associated with severity of total PTSD symptoms, but positively associated with...
PTSD’s dysphoric arousal symptoms, which suggests that long-term cortisone changes may be involved in the development and maintenance of PTSD symptoms. As the first study linking hair cortisone levels to a newly-refined and well-validated phenotypic model of PTSD symptoms, the current study contributes to limited literatures on long-term endocrine correlates of posttraumatic psychopathology, and extends extant knowledge on the probable role of stress-related hormone in relation to heterogeneous aspects of the complex phenotype of PTSD.

Cortisone is a main metabolite of cortisol, and the interaction between endogenous glucocorticoid cortisol and cortisone regulates stress-induced psychological and physiological responses together (Krumholz et al., 2013). Although cortisone has been proposed as a useful additional biomarker for stress research (Gatti et al., 2005; Krumholz et al., 2013; Vanaelst et al., 2013), only very limited studies investigated alterations of cortisone levels in PTSD patients compared with normal controls (Wheler et al., 2006) and after psychotherapy in PTSD patients (Yehuda et al., 2009). In the current study, we examined the associations between PTSD symptomatology and hair cortisone levels which can reflect cumulative cortisone secretion over prolonged periods of time and is more robust to the influence of situational confounding. An initial analysis showed that there were no significant differences in hair cortisone levels between PTSD cases and traumatized controls, which indicate that the basal cortisone secretion in hair could not distinguish traumatized individuals with and without PTSD well. In a recent study investigating the relationship between PTSD and hair cortisol, Steudte et al. (2013) reported that PTSD group only significantly differed from nontraumatized control group but not traumatized control group in term of hair cortisol levels, and hair cortisol levels were significantly associated with the number and frequency of traumatic experiences. Accordingly, Steudte et al. (2013) proposed that hair cortisol may be a biomarker of traumatization rather than PTSD. The current finding also suggests that hair cortisol may not be a biomarker of PTSD. As this study did not include a nontraumatized control group and used a highly traumatized sample exposed to specific disasters, we could not further specify whether hair cortisone may be a biomarker of traumatization. However, Vanaelst et al. (2013) recently reported that hair cortisone levels were significantly associated with the number of overall life events and negative life events for the past 6 months in a sample of elementary school girls, which provides indirect evidence supporting the proposition. Further studies on this interesting topic are needed.

PTSD is a complex and heterogeneous phenotype consisting of distinct symptom clusters, and empirical evidences support that the distinct symptom clusters may linked to different biological processes (Horn et al., 2014; Pietrzak et al., 2013a; Pietrzak et al., 2013b; Steudte et al., 2013). Based on a contemporary 5-factor phenotypic model of PTSD symptoms, the current study further examined how hair cortisone levels were link to heterogeneous symptom clusters of the PTSD phenotype. The results showed that hair cortisone levels were only significantly associated with dysphoric arousal symptoms, but not total PTSD symptoms and the other PTSD’s symptom clusters. Specifically, the higher hair cortisone levels were, the severer dysphoric arousal symptoms were. Due to the correlational nature of the association, the current data do not allow us to make a conclusive causal inference. As glucocorticoid drugs, cortisone and its derivatives have been extensively used to treat immune-related diseases in clinical settings. The negative psychological and somatic effects induced by cortisone treatment, as well as cortisone-related psychological and physiological responses, have received extensive attention (Clark et al., 1952; Brown and Chandler, 2001; Warrington and Michael Bostwick, 2006). Depending on the dose and duration of medication, irritability, concentration problems, and sleep disturbances which comprised of the dysphoric arousal symptom cluster were commonly reported psychological and somatic symptoms induced by cortisone drugs (Dubovsky et al., 2012; Monov and Monova, 2007; Ross and Cetas, 2012; Wolkowitz et al., 1990). These empirical evidences further confirm our finding of the positive association between cortisone levels and dysphoric arousal symptoms, and suggest that dysphoric arousal symptoms may be underpinned by upregulation of cortisone levels. Taken together, the current findings suggest that cortisone may play a critical role in mediating a key aspect of the complex PTSD phenotype—dysphoric arousal symptoms, and also provide further evidence supporting that dysphoric arousal is a unique PTSD construct. Considering the important role of dysphoric arousal symptoms in the development and maintenance of PTSD symptoms (Pietrzak et al., 2014), further studies focusing on the specific cortisone-related association may help specify the underlying biological mechanisms of post-traumatic stress symptomatology, and identify potential therapeutic targets for prevention and treatment of PTSD.

This study had several limitations. First, the generalizability of the findings was limited by our utilization of a sample exposed to specific traumatic stressors. Thus, the findings need to be further tested by additional studies with samples from populations exposed to a range of traumatic events. Second, the current findings were only yielded from females. Therefore, further replication of our findings with mixed male samples is required. Third, this study used a self-rated measure to assess PTSD symptoms. Further studies using clinician-rated measures are clearly warranted. Fourth, this study only focused on the five-factor phenotypic model of PTSD symptoms defined in the DSM-IV. Considering that the DSM-5 has been released with several significant modifications to PTSD criteria (APA, 2013), and several newly refined phenotypic models of DSM-5 PTSD symptoms have been proposed and validated (e.g., Armour et al., 2015; Liu et al., 2014a; Tsai et al., in press), future research should also aim to examine the utility of the DSM-5 based phenotypic models in this context.

In spite of these limitations, this is first study to investigate the relationships between hair cortisone levels and PTSD symptomatology. Our results indicated that although hair cortisone secretion could not distinguish traumatized individuals with and without PTSD, it was uniquely linked to dysphoric arousal symptoms, a key aspect of the complex PTSD phenotype in highly traumatized females. The findings provide preliminary evidence supporting the critical role of long-term cortisone changes in the development and maintenance of PTSD symptoms, and add to extant knowledge on the neuroendocrinological underpinnings of posttraumatic psychopathology.

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Conflict of interest
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