Hypothalamic–Pituitary–Adrenal Activity Among Armenian Adolescents With PTSD Symptoms

Armen K. Goenjian, Robert S. Pynoos, Alan M. Steinberg, David Endres, Khachik Abraham, Mitchell E. Geffner, and Lynn A. Fairbanks

This study evaluated basal levels and responsiveness to exercise of plasma adrenocorticotropic hormone (ACTH), and serum thyroid stimulating hormone (TSH), growth hormone (GH) and cortisol among adolescents from two differentially exposed groups 6 years after the 1988 earthquake in Armenia. Severity of total PTSD and Category C and D symptoms were negatively correlated with baseline cortisol. Preexercise ACTH was significantly lower, and preexercise TSH higher, among adolescents with more exposure. Depressive symptoms were negatively correlated with baseline cortisol and positively with TSH. Mean GH, TSH, and cortisol levels in both groups fell within normal limits. The pre- to postexercise increase in GH, TSH, and cortisol suggests that exercise challenge may be useful in the field investigation of neurohormonal activity among traumatized individuals.

KEY WORDS: trauma; PTSD; cortisol; ACTH; growth hormone; TSH.

Most studies of hypothalamic–pituitary–adrenal (HPA) related stress hormones among traumatized individuals have been conducted among adults. In regard to cortisol, studies have found lower basal urinary, serum, and salivary cortisol levels among adults (Boscarino, 1996; Mason, Giller, Kosten, Ostroff & Podd, 1986; Yehuda et al., 1990, 1995) and adolescents (Goenjian et al., 1996) with chronic posttraumatic stress disorder (PTSD) compared with controls. However, a number of other studies have found the opposite (Carrion et al., 2002; De Bellis et al., 1999; Lemieux & Coe, 1995; Pitman & Orr, 1990), while others have found no difference from controls (Baker et al., 1999; Kosten, Wahby, Giller & Mason, 1990). Studies have also documented a negative correlation between PTSD symptoms and salivary (Goenjian et al., 1996), serum (Baker et al., 1999), and urinary cortisol (Yehuda et al., 1995), and a positive correlation between PTSD symptoms and plasma cortisol (Smith et al., 1989). With regard to adrenocorticotropic hormone (ACTH), DeBellis et al. (1994) have reported lower basal plasma ACTH among sexually abused prepubescent girls with depression, whereas Smith et al. (1998) found a trend toward lower ACTH among combat veterans with chronic PTSD.

Both thyroid stimulating hormone (TSH) and growth hormone (GH) are secreted by the anterior pituitary gland, and both are implicated in the hormonal response to stress. Three studies among war veterans with PTSD have found no difference in baseline TSH in comparison with controls (Kosten et al., 1990; Mason et al., 1994; Wang & Mason, 1999). Bauer, Priebe, Kurten, Graf, and Baumgarner (1994) found lower serum TSH among East German Afghanistan Veteran

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refugees exposed to prolonged stress compared with controls. With regard to GH, civilian adults exposed to the Persian Gulf War showed no alterations in GH with changes in anxiety from pre- to postwar (Weizman et al., 1994). Similarly, patients with a diagnosis of noncombat-related PTSD showed no difference in GH compared with controls (Yatham, Sacamano & Kusumaker, 1996). Though less responsive to stress than cortisol, normal serum GH response to vigorous exercise has been used as a screening test for GH deficiency (Underwood & Van Wyk, 1992).

The 1988 earthquake in Armenia, known as the Spitak earthquake, registered 6.9 on the Richter scale, caused the destruction of 4 cities and 350 villages, killing at least 25,000 people in an area inhabited by 500,000 people. The adolescents in this study were from two cities, Spitak, the city at the epicenter, and Yerevan, a city at the periphery of the earthquake zone. Adolescents who had lived in Spitak, which was 90% destroyed with approximately 17% of the population killed, were classified as the high exposure group. Adolescents who had lived in Yerevan were classified as having experienced low exposure to the earthquake.

Five years after the earthquake, adolescents with chronic PTSD symptoms from Spitak, the city at the epicenter, manifested lower morning cortisol levels and hypersecretion of cortisol after dexamethasone (Goenjian et al., 1996). PTSD B category symptoms were significantly negatively correlated with basal morning cortisol levels, and with percent suppression by dexamethasone. This study was designed to determine whether low cortisol levels would be found among a different group of similarly highly exposed adolescents evaluated at 6½ years postearthquake. The study also evaluated other aspects of HPA axis activity, including ACTH, TSH, and GH.

To expose potential functional deficits, the effect of exercise challenge on these hormones was measured. The study also examined the interrelationship among these hormones, and their relation to PTSD and depression. We hypothesized that cortisol and ACTH levels would be significantly lower among the most exposed group, and that there would be a negative correlation between cortisol level and PTSD symptom severity. In regard to the other stress hormones investigated, this study was exploratory, not hypothesis-driven. These additional hormones were investigated because they are components of HPA-Axis functioning, which has been shown to be altered in PTSD.

Methods

Participants

Eighth-grade students from two representative schools, one in Spitak, a city at the epicenter, and one in Yerevan at the periphery of the earthquake zone, were recruited from their respective classrooms. This age group was selected because these adolescents were (1) old enough to have experienced and remember the earthquake, (2) were capable of reliably responding to the study instruments, and (3) would be available for follow-up studies before graduating from public school. All of the adolescents from Spitak were considered to have had severe exposure to trauma, whereas those from Yerevan were classified to have had low exposure to earthquake-related trauma. The students from both groups were of the same ethnic and religious background, and had resided in their respective cities during and since the earthquake. None of these adolescents were taking medications at the time of the study. All of the recruited 8th-grade students, except two from Yerevan, participated in the study. After having the study procedures explained, adolescents gave their assent, and one parent or guardian of each adolescent signed an informed consent form.

Demographic characteristics were: Spitak (N = 33), 17 boys, 16 girls (mean age = 14, SD = 0.5; mean height = 64 in., SD = 3.4 in.; mean weight = 117 lbs., SD = 18 lbs.); Yerevan (N = 31), 15 boys, 16 girls (mean age = 14, SD = 0.3; mean height = 63 in., SD = 2.8 in.; mean weight = 110 lbs., SD = 19 lbs.). None of these variables was significantly different between the two groups.

Measures

PTSD symptoms were rated using the self-report Child Posttraumatic Stress Disorder Reaction Index (CPTSD-RI), a widely used 20-item self-report inventory in which symptom frequency is rated using a 0–4 Likert frequency scale. Prior comparisons of CPTSD-RI scores with a diagnosis of PTSD in clinical populations have suggested the following guidelines: 0–11 = doubtful; 12–24 = mild; 25–39 = moderate; 40–59 = severe; 60–80 = very severe (Nader, Pynoos, Fairbanks, & Frederick, 1990). Previous findings have indicated that a score of 40 or above is highly associated with PTSD diagnosis (Pynoos et al., 1993). Depressive symptoms were rated using the Depression Self-Rating Scale (DSRS; Asarnow & Carlson, 1985), a 24-item self-report instrument with item frequency rated 0 = never; 1 = sometimes; 2 = most of the time. A score of 17 or above is highly associated with a diagnosis of major depression, dysthymic disorder, or adjustment disorder with depressed mood. Translation procedures and psychometric properties for both of these instruments as used in this population have been previously described (Pynoos et al., 1993).
HPA Activity in Traumatized Adolescents

**Procedure**

Participants were clinically evaluated on the day before drawing blood. After overnight fasting, 9 a.m. blood was drawn. Subsequently, participants jogged for 15 min. and then ran vigorously for 5 min. according to guidelines for evaluating GH response to exercise challenge (Underwood & Van Wyk, 1992). A second needle stick was performed to draw a second blood 20 min after exercise. Tubes were placed on ice, centrifuged within 30 min, and shipped on dry ice for analysis.

**Assays**

EDTA plasma ACTH was measured by immunoradiometric assay (IRMA) for intact ACTH (Nichols Institute Diagnostics). The method has a limit of detection of 1 pg/ml and a normal range (7–10 a.m.) of 7–52 pg/ml. The within- and between-assay coefficients of variation are 3.0% at 35 pg/ml and 7.8% at 36 pg/ml, respectively. Serum cortisol levels were measured using solid-phase IRMA based on monoclonal and polyclonal antibodies (Diagnostic Products Corp., Los Angeles, CA). Serum TSH levels were measured using solid-phase IRMA based on monoclonal and polyclonal antibodies (Diagnostic Products Corp., Los Angeles, CA). Serum GH was measured by using IRMA for human GH (Tandem-R, Hybritech). This method has a limit of detection of 0.2 ng/ml. The within- and between-assay coefficients of variation are 3.8% at 5.1 ng/ml and 5.2% at 7.8 ng/ml, respectively.

**Statistical Analysis**

Student’s t-tests were used to compare groups with regard to demographic and clinical variables. Because of the presence of outliers within some of the hormone categories, Mann–Whitney Z tests were performed to compare the groups in regard to hormone levels. Wilcoxon Signed Ranks Tests were used to compare pre- to postexercise change in hormone levels. Spearman correlation was used to assess interrelationships among the clinical and biological variables.

**Results**

Table 1 shows the mean pre- and postexercise values for neurohormonal variables for subjects in Spitak and Yerevan.

Mean CPTSD-RI score was significantly higher in Spitak (35.2, SD = 13.6), with scores falling in the upper moderate range, and scores in Yerevan (25.7, SD = 11.1) falling in the lower moderate range, t(61) = 3.1, p < .01. Mean DSRS score did not differ significantly between groups: Spitak = 15.5, SD = 6.2; Yerevan = 13.2, SD = 6.0; t(62) = 1.5, ns, with both groups falling a few points below the clinical cutoff for depression. Preexercise cortisol levels were not significantly different between the groups (Z = .58, N = 64, ns). Preexercise ACTH level was significantly lower in Spitak (Z = 4.56, N = 64, p < .001), with the mean slightly below the normal limit. Preexercise TSH level was significantly higher in Spitak (Z = 2.90, N = 64, p < .01), though both groups were within normal limits. There was a trend for preexercise GH level to be higher in Spitak compared to Yerevan (Z = 1.85, N = 64, p = .06). Both preexercise means fell in the normal range. For all subjects combined, there was a significant preto postexercise increase in, cortisol (Z = −3.19, N = 64, p < .01), TSH (Z = −3.54, N = 63, p < .001), and GH (Z = −5.47, N = 64, p < .001), but not for ACTH (Z = −1.22, N = 62, ns). Comparison of the change in pre- to postexercise hormone levels between Spitak and Yerevan revealed that there were no significant differences for all hormones studied.

For the combined groups, CPTSD-RI score was positively correlated with DSRS score, r(63) = .56, p < .01, and negatively correlated with baseline cortisol, r(63) = −.33, p < .01. Baseline cortisol level was negatively correlated with PTSD Category C, r(63) = −.27, p < .05, and Category D scores, r(63) = −.30, p < .05, and marginally missed significance with category B scores, r(63) = −.24, p = .06. DSRS score was negatively correlated with demographic and clinical variables. Because of the presence of outliers within some of the hormone categories, Mann–Whitney Z tests were performed to compare the groups in regard to hormone levels. Wilcoxon Signed Ranks Tests were used to compare pre- to postexercise change in hormone levels. Spearman correlation was used to assess interrelationships among the clinical and biological variables.

**Table 1. Pre- and Postexercise Neurohormonal Measurements Among Adolescents 6 Months Years After the Earthquake in Armenia**

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<thead>
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<th>Hormone</th>
<th>Norm</th>
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<tbody>
<tr>
<td>Growth Hormone (0–10 ng/ml)</td>
<td>3.1</td>
<td>4.5</td>
<td>1.3–18.4</td>
<td>6.8</td>
<td>5.6</td>
<td>6.6–26.5</td>
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<td>TSH (0.3–5 μU/ml)</td>
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<td>Cortisol (5–25 μg/dl)</td>
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correlated with baseline cortisol, \( r(64) = -.40, p < .001 \), and positively with baseline TSH, \( r(64) = .28, p < .05 \). Baseline cortisol and ACTH were positively correlated, \( r(64) = .37, p < .01 \).

There were no significant effects of sex, and no sex by city interactions, for any of the clinical or hormone variables, including change in hormone levels from pre- to postexercise.

Discussion

The finding of a negative correlation of basal cortisol among adolescents with PTSD symptoms supports one of our hypotheses, and extends our previous finding of lower baseline salivary cortisol levels among more symptomatic Armenian adolescents at 5-years postearthquake (Goenjian et al., 1996). The present finding is also similar to ones reported among adults (Baker et al., 1999; Yehuda et al., 1995), and lends support to the hypothesis that individuals with PTSD have enhanced negative feedback inhibition resulting in lower cortisol levels (Yehuda, 2001).

Despite the negative correlation, there was no significant difference in mean basal cortisol level between the two differentially exposed groups. This finding did not confirm another of our hypotheses. However, the finding of a negative correlation with no group difference is similar to a finding reported by Baker et al. (1999) among veterans. Yehuda et al. (1995) reported lower urinary cortisol excretion among Holocaust survivors with chronic PTSD compared to survivors without PTSD, and suggested that exposure to trauma per se may not be associated with lower cortisol levels. The fact that other studies have found group differences may be attributable to the variability across studies in severity and chronicity of PTSD symptoms, and severity of comorbid depression between groups.

The equal positive cortisol response to exercise challenge between groups suggests that adrenal function may not be compromised among this group of adolescents with higher levels of chronic PTSD symptoms. However, it remains possible that a group difference in basal cortisol and cortisol response to exercise may have emerged if the mean CPTSD-RI scores between the groups had been greater.

The present findings with regard to correlations between baseline cortisol and PTSD symptom category scores are consonant with the Yehuda et al. (1995) finding among adults of a negative correlation of cortisol level with C category symptoms. However, this study also found a similar negative correlation with D category symptoms, and a trend in this regard for B category symptoms. Baker et al. (1999) reported a similar correlation with regard to Categories B and D, and a trend for Category C. The variations in correlations of PTSD symptom category scores with cortisol level may reflect the phasic course of PTSD symptoms, and differences between study populations in regard to type of trauma and time since trauma.

To our knowledge, this is the first report of ACTH levels and ACTH response to exercise challenge among adolescents after a disaster. The significantly lower basal ACTH levels among adolescents in the most traumatized group is consistent with the findings of De Bellis et al. (1994) among sexually abused girls. However, this finding needs replication with a larger sample, along with concomitant CRF and cortisol measurement. Findings of no difference in cortisol levels between subjects and controls in the De Bellis et al.’s study, and no difference between differentially exposed groups in the present study, against a background of low ACTH, is consistent with the proposed hyperresponsivity of the pituitary to cortisol by increased glucocorticoid receptor number or responsiveness (Yehuda, 2001), accompanied by adrenal hyperresponsivity.

Unlike the attenuated response of ACTH to CRH challenge among sexually abused girls (DeBellis et al., 1994), this did not demonstrate any ACTH response to exercise challenge among either the adolescents in Yerevan, or among the highly exposed adolescents in Spitak. However, exercise may not have been an adequate challenge to expose this phenomenon.

The present finding of significantly higher basal TSH levels among the more highly exposed group is discordant with findings among veterans with chronic PTSD (Mason et al., 1994; Wang & Mason, 1999) who showed no difference from controls. However, in both the present and these prior studies, TSH levels were well within the normal clinical range. The higher TSH levels in Spitak may reflect an age-related trauma sensitive vulnerability to alteration in pituitary activity, or may be associated with comorbid depression, as suggested by the significant positive correlation of TSH with depression, and not PTSD symptoms, in this study. This latter finding compliments the finding of elevated nocturnal TSH secretion among depressed adolescents (Kutcher, Malkin, & Silverberg, 1991) and elevated serum TSH levels among patients with endogenous depression (Kirkegaard, Korner, & Faber, 1990). Longitudinal assessments of T3 and T4 levels along with TSH would help to determine whether the source of an elevated TSH is primary or secondary in origin.

The finding that both groups had normal GH levels extends prior findings among traumatized adults (Yatham et al., 1996). The normal levels among adolescents from Spitak, coupled with their response to exercise challenge in the absence of significant differences in height and
weight between the groups, suggests that this aspect of their putative function is intact.

As reported among normal adults (Bosco et al., 1996), this study, combining all participants, demonstrated the effect of exercise in increasing GH, TSH, and cortisol among adolescents. The study indicates that this methodology can be applied in the field, and may be useful in the investigation of neuroendocrine function among traumatized individuals. The study demonstrates the advantage of child trauma experts working collaboratively with pediatric endocrinologists.

References


