# Corticotropin-Releasing Factor, Interleukin-6, Brain-Derived Neurotrophic Factor, Insulin-Like Growth Factor-1, and Substance P in the Cerebrospinal Fluid of Civilians With Posttraumatic Stress Disorder Before and After Treatment With Paroxetine

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***Background:*** Posttraumatic stress disorder (PTSD) is associated with altered concentrations of stress-related neurohormones, neurotrophins, and neuropeptides in plasma and serum; however, few studies have examined central alterations of these measures in individuals with PTSD. Furthermore, no study to date has evaluated the effects of successful antidepressant treatment on cerebrospinal fluid (CSF) abnormalities in PTSD.

***Method:*** Sixteen medication-free outpatients with chronic PTSD (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria) due to physical and/or sexual abuse or motor vehicle accidents (mean ± SD age = 36 ± 11.4 years, 12 women) and 11 nontraumatized healthy subjects (mean ± SD age = 35.3 ± 13.1 years, 7 women) underwent a lumbar puncture for collection of CSF. Seven PTSD patients had a repeat lumbar puncture 12 weeks later, after successful treatment of PTSD with paroxetine. CSF was analyzed for corticotropin-releasing factor (CRF), interleukin-6 (IL-6), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and substance P concentrations. The study was conducted between January 2003 and August 2004.

***Results:*** Compared to nontraumatized healthy controls, patients with chronic PTSD had similar pretreatment concentrations of CSF CRF, IL-6, BDNF, IGF-1, and substance P. Posttreatment CSF measures did not change significantly in patients whose symptoms remitted with paroxetine.

***Conclusions:*** Chronic, moderate PTSD due to civilian trauma, without psychotic symptoms and without significant rates of comorbid depression, alcohol dependence, or substance dependence, is not associated with abnormalities in CSF CRF, IL-6, BDNF, IGF-1, or substance P levels. Despite substantial reduction in PTSD symptoms, antidepressant treatment does not alter normal central concentrations of these neurochemicals, with the possible exception of substance P.

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Considerable evidence links abnormalities in stress-related neurohormones, neurotrophins, and neuropeptides to posttraumatic stress disorder (PTSD). Corticotropin-releasing factor (CRF) is the main stimulator of the hypothalamic-pituitary-adrenal (HPA) axis, and it plays a vital role in coordinating behavioral, immune, and autonomic responses to stress. However, findings regarding central CRF concentrations in PTSD are inconsistent. While combat-related PTSD has been associated with increased concentrations of CRF in cerebrospinal fluid (CSF),[1,2] at least 1 other study noted that CSF CRF was elevated only in a subgroup of combat veterans with PTSD and secondary psychotic symptoms but not in veterans with PTSD without psychotic symptoms or healthy nontraumatized controls.[3] Furthermore, in contrast to prior reports of elevated basal concentrations, stress levels of CSF CRF paradoxically decreased during trauma reminders in a similar sample of combat veterans with PTSD.[4]

Posttraumatic stress disorder has also been associated with increased concentrations of plasma and CSF interleukin-6 (IL-6), a proinflammatory cytokine.[5,6] Stress is known to reduce concentrations of brain neurotrophins, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1). Patients with mood disorders or those who have experienced physical and sexual abuse or neglect also have lower plasma BDNF concentrations.[7–9] In addition, 3 weeks of stressful combat training has been shown to significantly reduce plasma IGF-1.[10] Although stress-induced decreases in neurotrophic factors offer a potential mechanism for the smaller hippocampal volumes associated with PTSD,[11] prior studies have not assessed CSF concentrations of BDNF or IGF-1 in individuals with PTSD.

Preclinical studies in rats[12] and clinical research in patients with major depressive disorder (MDD)[13,14] confirmed that antidepressant treatment reversed HPA axis abnormalities and decreased CSF CRF concentrations. Chronic treatment with antidepressants increased CSF and prefrontal concentrations of BDNF[15] and enhanced the expression of IGF-1 messenger RNA[16] in rats. Plasma BDNF concentrations have also been noted to increase in depressed patients who responded to antidepressant treatment.[17] Successful treatment of PTSD symptoms with antidepressants

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reduced concentrations of interleukin-1β, another proinflammatory cytokine.[18] While serum concentrations of substance P decreased in depressed patients who responded to antidepressant treatment,[19] CSF levels of substance P remained unchanged despite 35 days of antidepressant treatment.[20] In PTSD, CSF substance P concentrations are increased,[21] although it is presently unknown whether successful treatment alters this abnormality. It is also unknown whether the CSF CRF and IL-6 abnormalities seen in individuals with PTSD are persistent trait markers of the disorder or are state markers that normalize with successful treatment of symptoms. Although some studies have noted hippocampal volume increases after successful treatment of PTSD with paroxetine,[22] no studies have evaluated whether central neurotrophin concentrations increase after remission of PTSD symptoms.

The present study compared pretreatment concentrations of CSF CRF, IL-6, BDNF, IGF-1, and substance P between civilian patients with PTSD and nontraumatized healthy controls. We then sought changes in these measures in patients with PTSD after successful treatment with paroxetine, a selective serotonin reuptake inhibitor (SSRI). We hypothesized that patients with PTSD due to civilian trauma would have higher concentrations of CSF CRF, IL-6, and substance P and lower concentrations of CSF BDNF and IGF-1 than nontraumatized healthy controls. We further hypothesized that these abnormalities would be reversed after successful treatment of PTSD with paroxetine.

## METHOD

### Participants

Sixteen medication-free outpatients with chronic PTSD (mean ± SD age = 36 ± 11.4 years, 12 women) and 11 nontraumatized, healthy subjects (mean ± SD age = 35.3 ± 13.1 years, 7 women) gave informed consent to participate in the study, using procedures established by the National Institutes of Health Institutional Review Board. Patient traumas were not combat-related and occurred either prepubertally (n = 7) or as adults (n = 9; see Table 1). The mean ± SD time elapsed from exposure to trauma to study participation was 26 ± 4 years in patients exposed to prepubertal trauma and 10.1 ± 8.8 years in patients with adult exposure. Patients were physically healthy, had received no psychotropic medications for at least 3 weeks before the lumbar puncture (6 weeks for fluoxetine), and did not meet criteria for alcohol or substance abuse or dependence for at least 6 months prior to the study. The study was conducted between January 2003 and August 2004 under the aegis of the Mood and Anxiety Disorders Program at the National Institute of Mental Health, Bethesda, Maryland.

Psychiatric diagnoses were established using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-CV),[23] and the severity of PTSD was determined using the Clinician-Administered PTSD Scale (CAPS).[24] Severity of depressive and anxiety symptoms was assessed using the Inventory of Depressive Symptomatology (IDS)[25] and Hamilton Anxiety Rating Scale (HARS).[26]

**Table 1. Sociodemographic, Clinical, and Trauma Variables in Patients With PTSD and Healthy Controls[a]**

| Variable | PTSD Patients (n = 16) | Healthy Controls (n = 11) | *P* Value |
|---|---|---|---|
| Sociodemographic | | | |
| Age, y | 36.1 (11) | 35.3 (13.1) | .59 |
| Sex, female, n (%) | 12 (75.0) | 7 (63.6) | .41 |
| Race, n | | | .27 |
| White | 9 | 8 | |
| African American | 4 | 2 | |
| Other | 3 | 1 | |
| Clinical | | | |
| Total CAPS score, pretreatment | 74.5 (11.8) | NA | NA |
| Total CAPS score, posttreatment | 12 (8.4) | NA | NA |
| IDS score, pretreatment | 17.8 (8.9) | 1.2 (.86) | .003 |
| IDS score, posttreatment | 6.4 (3.4) | NA | NA |
| HARS score, pretreatment | 13.3 (7.0) | 1.5 (.9) | .001 |
| HARS score posttreatment | 8.8 (3.9) | NA | NA |
| Body mass index, kg/m$^2$ | 26.7 (6.5) | 24.9 (5.8) | .68 |
| Current GAD + specific phobia, n | 1 | 0 | .173 |
| Current MDD, n | 2 | 0 | .065 |
| Past MDD, n | 8 | 0 | .01 |
| Past substance abuse/ dependence, n/n | 0/1 | 0/1 | 1.00 |
| Past alcohol abuse/ dependence, n/n | 0/1 | 0/0 | .17 |
| Current smoking | 1 | 1 | 1.00 |
| Trauma, n | | | |
| Prepubertal trauma | 7 | 0 | NA |
| Sexual abuse | 3 | 0 | NA |
| Physical abuse | 4 | 0 | NA |
| Adult trauma | 9 | 0 | NA |
| Motor vehicle accident | 5 | 0 | NA |
| Sexual assault | 2 | 0 | NA |
| Physical assault | 2 | 0 | NA |

[a]When not otherwise specified, data are presented as mean (SD).
Abbreviations: CAPS = Clinician-Administered PTSD Scale, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, IDS = Inventory of Depressive Symptomatology, MDD = major depressive disorder, NA = not applicable, PTSD = posttraumatic stress disorder.

Raters were experienced mental health research professionals, who served as the case-managing clinicians and were not blind to the diagnoses of the patients. Control participants were healthy and medication-free and had no significant current or past medical or psychiatric illness, with the exception of 1 participant who had a remote history of substance dependence.

Sociodemographic and clinical characteristics for PTSD patients (before and after treatment) and controls are given in Table 1. Individuals with PTSD and controls did not differ with regards to age, sex distribution, race, or body mass index (BMI).

### Lumbar Puncture

The lumbar puncture was performed between 8:00 and 9:00 AM by an experienced physician. Briefly, a 20-gauge introducer needle was inserted, and approximately 15 cc of CSF was withdrawn and frozen at −80°C until batch assayed. One PTSD patient's pretreatment CSF sample could not be analyzed due to technical difficulties; therefore his posttreatment CSF values were not included in the final analysis. In addition, only 4 subjects had sufficient CSF volume to enable both pre– and post–substance P–level comparisons.

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**Table 2. CSF Neurohormone, Neurotrophin, and Neuropeptide Concentrations in Healthy Controls and Medication-Free Patients With PTSD**

| Concentration | Healthy Controls (n = 11), Mean (SD) | PTSD Patients (n = 15), Mean (SD) | Statistic | | |
|---|---|---|---|---|---|
| | | | *t* | *df* | *P* |
| BDNF, pg/mL | 0.83 (.44) | 1.00 (.52) | 0.88 | 24 | .39 |
| IL-6, pg/mL | 1.45 (.52) | 1.25 (.49) | −1.00 | 24 | .33 |
| CRF, pg/mL | 25.4 (13.6) | 21.0 (8.3) | −1.01 | 24 | .32 |
| IGF-1, ng/mL | 109.4 (61.6) | 102.1 (42.8) | −0.36 | 24 | .72 |
| Substance P, fmol/mL | 70.5 (44.8) | 70.4 (39.5) | −0.01 | 22 | .99 |

Abbreviations: BDNF = brain-derived neurotrophic factor, CRF = corticotrophin-releasing factor, IGF-1 = insulin-like growth factor-1, IL-6 = interleukin-6.

**Table 3. CSF Measures Before and After Successful Treatment of PTSD With Paroxetine, a Selective Serotonin Reuptake Inhibitor**

| CSF measure | Pretreatment/ Posttreatment Pairs, No. | Pretreatment, Mean (SD) | Posttreatment, Mean (SD) | Statistic | | |
|---|---|---|---|---|---|---|
| | | | | *t* | *df* | *P*[a] |
| BDNF, pg/mL | 7 | 0.77 (.36) | 0.74 (.38) | −0.31 | 6 | .77 |
| IL-6, pg/mL | 7 | 1.30 (.64) | 1.33 (.52) | 0.21 | 6 | .84 |
| CRF, pg/mL | 7 | 21.8 (11.1) | 18.9 (9.4) | −1.21 | 6 | .27 |
| IGF-1, ng/mL | 7 | 113.6 (47.7) | 104.3 (38.4) | −1.51 | 6 | .18 |
| Substance P, fmol/mL | 4 | 54.5 (18.7) | 29.6 (15.6) | −4.24 | 3 | .02 |

[a] *P* values represent comparisons before Bonferroni correction. No comparisons retained significance after Bonferroni correction was applied.
Abbreviations: BDNF = brain-derived neurotrophic factor, CRF = corticotrophin-releasing factor, IGF-1 = insulin-like growth factor-1, IL-6 = interleukin-6.

### Paroxetine Treatment

All 16 PTSD patients were offered a 12-week course of open-label treatment with paroxetine, and 12 agreed to participate. Of these 12, 10 completed the treatment course. Treatment was started at a dose of 20 mg/d and increased to 40 mg/d if clinical improvement was not satisfactory after 1 month of treatment (mean ± SD paroxetine dose = 33.3 ± 6.5 mg/d). All completers achieved complete remission (defined as a CAPS score of less than 50) and no longer met SCID criteria for PTSD, with an 86% decrease in CAPS score and a 64% decrease in IDS score (see Table 1). Seven of the 10 treatment responders underwent a repeat lumbar puncture, and 3 refused the second lumbar puncture procedure.

### Laboratory Assays

Cerebrospinal fluid was aliquoted and frozen at −80°C until batch assayed. Corticotropin-releasing factor was measured in quadruplicate 50-µL aliquots of CSF by non-equilibrium radioimmunoassay using a high-affinity antibody (S-2021, raised in rabbit against human CRF) and materials from Bachem Americas Inc (Torrance, California). Antibody (25 µL) was added to the CSF, and the mixture was incubated under saturated humidity at 2°C for 24 h. Trace $^{125}$I-tyr0-CRF (25 µL) was then added and the mixture incubated for a further 16 h. The CRF-antibody complex was precipitated using goat-antirabbit immunoglobulin G, normal rabbit serum and 5% polyethylene glycol. Under the supervision of M.J.O., sensitivity (blank + 2 SD) was assessed at 2.8 pg/mL, and the coefficient of variation (SD/mean) between quadruplicate was 7.5%. The assay exhibited an intraassay variability of less than 9% and an interassay variability of less than 10%. Aliquot volume was 400 mL, and sensitivity was 5.0 pg/tube, with 50% displacement. Interleukin-6 was measured using a specific high-sensitivity solid-phase enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minnesota) under the supervision of P.Y. The assay exhibited intraassay and interassay coefficients that ranged from 5.6%–6.1% and from 7.5%–10.4%, respectively. Aliquot volume was 400 mL, and sensitivity was 4.25 pg/tube, with 50% displacement. Brain-derived neurotrophic factor analysis was also undertaken by P.Y. Concentration was determined using a ChemiKine BDNF Sandwich ELISA Kit (Chemicon, Temecula, California); both intraassay and interassay variability were within 10%. Aliquot volume was 450 mL, and sensitivity was 7.8 pg/tube, with 50% displacement. Substance P concentration was determined by B.K. with a solid-phase radioimmunoassay using a highly specific substance P antibody (Fisher Scientific, Pittsburgh, Pennsylvania); intraassay variability was 8.2%, and interassay variability was 9.7%. Aliquot volume was 450 mL, and the sensitivity was 100 fmol/mL, with 50% displacement.

### Statistics

Independent *t* tests were used to compare PTSD patients and controls on continuous measures, and $\chi^2$ tests were used for categorical measures. Pretreatment and posttreatment comparisons were made with paired *t* tests and included only patients with both pretreatment and posttreatment values. Pearson *r* was used for correlations. Outliers, defined as having a value greater than 3 SDs from the mean, were removed from the analysis.

## RESULTS

Civilian patients with chronic PTSD had concentrations of CRF, IL-6, BDNF, IGF-1, and substance P similar to healthy controls (Table 2). The results were unchanged after removing an outlier in the CSF CRF values in the healthy control group. Severity of PTSD symptoms, measured by baseline CAPS scores, tended to be positively correlated with baseline CSF CRF concentrations ($r = 0.44$, $P = .097$); however, all other correlations between clinical variables and other CSF measures were not significant.

No significant change in CSF CRF, IL-6, BDNF, IGF-1, and substance P was observed after successful remission of PTSD symptoms after paroxetine treatment. A reduction in substance P concentration after treatment in a subset of 4 patients with PTSD was no longer significant after correcting for multiple comparisons (Table 3). Correlations between pretreatment and posttreatment neuromodulator concentrations were significant for IL-6 ($r = 0.98$, $P = .003$), CRF ($r = 0.80$, $P = .03$), and IGF-1 ($r = 0.75$, $P = .05$); a trend in this direction was observed for BDNF concentrations ($r = 0.68$,

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$P = .09$). Cerebrospinal fluid measures were not associated with subtype of trauma, age at trauma, severity of depression, or alcohol/substance use.

## DISCUSSION

This study is the first to assess CSF concentrations of neuroendocrine, neurotrophin, and neuropeptide measures in chronic PTSD related to *civilian,* rather than combat-related, trauma. We found that medication-free civilians with chronic PTSD and nontraumatized healthy controls had similar CSF concentrations of CRF, IL-6, BDNF, IGF-1, and substance P. In patients with PTSD, CSF concentrations of these neurochemicals were unchanged after paroxetine-induced remission of symptoms.

Results from the present study differ from the majority of previous reports of basal elevations of CSF concentrations of CRF,[1–3] substance P,[21] and IL-6[5] in veterans with chronic PTSD. In contrast to all prior CSF studies in PTSD, the present study instead assessed an exclusively civilian sample of primarily women with chronic PTSD after physical and/or sexual abuse or motor vehicle accidents; almost half of these patients reported prepubertal trauma as the precipitating event. Our sample also had less severe PTSD symptoms and fewer psychiatric comorbidities than samples used in many previous studies.[1,2] (Only 2 of the 16 patients had concurrent MDD, 2 had a past history of either alcohol or substance dependence, 1 patient was a smoker, and none of the patients had secondary psychotic symptoms.) Differences in the timing of sample collection between our study and others could also explain the discrepancy in our results. In this study, a single sample of CSF was collected between 8:00 AM and 9:00 AM, in contrast to Baker and colleagues,[1] who collected multiple CSF samples between 11:00 AM and 5:00 PM. Watching a stressful combat video lowered CSF CRF concentrations in combat veterans with PTSD, suggesting altered stress responsiveness in PTSD.[4] It is therefore possible that the anticipation of a stressful lumbar puncture could have influenced CSF neurochemicals, particularly CSF CRF, in the present study. Because BMI can influence CSF CRF concentrations, both our study and the one by Baker and colleagues[1] covaried for differences between groups; however, other studies did not take this additional factor into account. Our CSF CRF findings however, resemble those of Sautter et al,[3] who demonstrated that combat veterans with chronic PTSD without psychotic symptoms had similar CSF CRF levels as healthy controls. This similarity provides further evidence that psychiatric comorbidities influence CRF findings and must be considered when comparing studies.

Since stress-related reductions in CSF BDNF and IGF-1 concentrations have been observed in animal studies and offer a potential mechanism for the smaller hippocampal volumes associated with PTSD and MDD, the lack of difference observed between PTSD patients and healthy controls on these measures in the present study is surprising.[22] It is possible that lower central concentrations of neurotrophic agents and perhaps related smaller hippocampal volume may be limited to individuals with more severe combat-related, chronic PTSD,[27,28] with comorbid conditions including alcohol dependence.[29]

Contrary to our original hypothesis, we detected no significant changes in CSF biomarker concentrations after successful antidepressant treatment for PTSD. It is also possible that the effects of antidepressants on biological variables evaluated in this study were not detectable given the lack of baseline differences between patients with PTSD and nontraumatized controls.

Although we did find a decrease in concentrations of CSF substance P after treatment with the SSRI paroxetine, this observation included only 4 PTSD subjects, and the decrease did not remain significant after Bonferroni correction. Nonetheless, because this decrease in substance P was compatible with previous reports,[19,20] and because the effect size observed was rather large ($d = -4.90$), future, appropriately sized studies should be conducted to evaluate changes in substance P concentrations after successful treatment of PTSD.

The treatment response rates and improvement in PTSD and depressive symptoms after paroxetine treatment in the present study were greater than previously observed in SSRI treatment trials in combat veterans[30–32] and civilian PTSD patients.[33] It is possible that the open-label design of paroxetine administration in the present study and a second similar study in civilian PTSD[22,34] accounted for these impressive treatment response rates.

This study was limited by the relatively small sample size, which may have affected our ability to detect significant baseline differences in CSF measures between patients with PTSD and controls, thereby reducing our ability to determine antidepressant effects. This may particularly apply to our finding of a trend toward reduced CSF substance P concentrations after treatment of PTSD patients with paroxetine. However, it is also possible that individuals with moderate PTSD after civilian trauma, without secondary psychotic symptoms or significant rates of comorbid depression and alcohol or substance abuse/dependence, are unlikely to have the significant abnormalities previously observed in central concentrations of CRF, IL-6, BDNF, IGF-1, and substance P. It has been established that more severe depressive symptoms, as measured by clinical rating scales for depression, are associated with increases in CSF concentration of CRF, and the correlations with PTSD symptoms and individual CRF concentrations echo this finding in this population. A similarly designed study needs to be undertaken in subjects with severe PTSD.

***Drug names:*** fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others).

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