

Elevated Cerebrospinal Fluid Substance P Concentrations in Posttraumatic Stress Disorder and Major Depression

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Objective: The authors tested the hypothesis that concentrations of the pain-transmitting neuropeptide substance P are elevated in the CSF of patients with major depression or posttraumatic stress disorder (PTSD), which have overlapping symptoms. The authors also sought to determine if CNS substance P concentrations change on provocation of symptoms in PTSD patients.

Method: The authors measured CSF substance P concentrations in medication-free patients with either major depression or PTSD and in healthy comparison subjects. Next, using a within-subject, cross-over design, the authors sampled CSF for 6 hours through an indwelling subarachnoid catheter in PTSD patients before, during, and after exposure to a 60-minute traumatic or neutral videotape stimulus.

Results: Both depressed and PTSD patients had significantly elevated basal CSF

substance P concentrations. In the challenge study, marked increases in CSF substance P concentrations were found only after precipitation of PTSD symptoms. CSF substance P concentrations increased by 169% and 90.6% of baseline levels at 10 and 70 minutes, respectively, after the start of the traumatic videotape but changed by only 1.1% and -8.1% of baseline levels 10 and 70 minutes after the start of the neutral videotape.

Conclusions: These results suggest that elevated CNS substance P concentrations are involved in both major depression and PTSD. The marked increase in CSF substance P concentrations during and after the symptom-provoking stimulus, but not after the neutral stimulus, implicates CNS release of substance P in the mechanism of acute PTSD symptoms. These data also reveal that CNS substance P responds acutely to psychological stress in humans.

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In 1931, Von Euler and Gaddum (1) analyzed extracts from equine organ systems and identified an active entity from the brain and intestines (but not from 10 other organs tested) that they termed extract or powder P; the substance was found to have potent hypotensive effects in atropinized rabbits anesthetized with ether. Numerous experiments over subsequent decades led to the characterization of an 11-amino acid peptide, substance P (2), now recognized to be the preferred ligand at the neurokinin-1 receptor (3, 4). Human CNS tissue exhibits a heterogeneous distribution of neurokinin-1 receptors that is especially enriched throughout the spinal cord, brainstem, and limbic system (5-11). Among its many actions, substance P has a major role in facilitating or transmitting nociceptive and stressful stimuli in the CNS (12-14).

In depressed humans, the substance P (neurokinin-1) antagonist MK-869 was reported to be an effective antidepressant in a double-blind, placebo-controlled trial (15), although subsequent clinical trials failed to confirm this finding (16). However, another substance P antagonist, L-759274, did exhibit antidepressant effects in a controlled clinical trial (17). In a postmortem study of human brains, Stockmeier et al. (18) observed a decreased density of neurokinin-1 receptors in the orbitofrontal cortex of individuals

who died by suicide and individuals with major depression, compared with individuals who were reportedly "psychiatrically normal," raising the possibility of chronic hypersecretion of substance P and subsequent down-regulation of these neurokinin-1 receptors.

Despite the ongoing testing of substance P antagonists in clinical trials for the treatment of depression, evidence of CNS substance P abnormalities in patients with major depression and/or PTSD is lacking. The measurement of CSF substance P concentrations in depressed patients is a remarkably understudied area, with findings (almost two decades old) of both elevated (19) and diminished (20) CSF concentrations of substance P-like immunoreactivity. Moreover, until the investigations reported herein, to our knowledge, there have been no studies of CSF substance P in PTSD or in any anxiety disorder.

Major depression and posttraumatic stress disorder (PTSD) are common and severe psychiatric syndromes that share risk factors (such as early life adversity), have overlapping symptoms (such as dysphoria and anxiety), frequently occur together, and are associated with high suicide rates. Pathophysiologically, both melancholic depression and PTSD are associated with elevated CSF concentrations of corticotropin-releasing hormone (CRH)

and norepinephrine (21–25), but only the former syndrome is characterized by hypercortisolemia (26). On the basis of the extant preclinical and clinical literature (12), the posited shared CNS pathophysiological mechanisms for depression-spectrum disorders and PTSD, and the clinical overlap between the syndromes, we hypothesized that CSF concentrations of the undecapeptide substance P are elevated in both conditions.

To measure CNS concentrations of substance P in depression and PTSD, we performed a series of CSF sampling experiments. First, using standard lumbar puncture, we measured CSF substance P concentrations in drug-free depressed patients (N=40) and healthy comparison subjects (N=47). Next, we collected CSF for 6 hours by means of an indwelling subarachnoid catheter in the spinal canal from eight drug-free, male military veterans with post-combat PTSD and from healthy comparison subjects. We waited approximately 3 hours after the placement of the subarachnoid catheter before beginning to withdraw CSF in order to control for the stress-related effects of needle insertion into the spinal canal (27). Finally, in a crossover symptom provocation study, an additional seven drug-free combat veterans with chronic PTSD completed 6-hour CSF sampling procedures on two occasions each (6–9 weeks apart) in which patients watched in random order either a 1-hour film containing combat footage from the Vietnam War (traumatic stimulus) or a 1-hour instructional film on oil painting (neutral stimulus).

Method

These studies were approved by the Institutional Review Boards of the University of Cincinnati Medical Center (Cincinnati) and Butler Hospital (Providence, R.I.), the Human Investigations Committee of Yale University School of Medicine (New Haven, Conn.), and the Research and Development Committee of the Cincinnati Veterans Affairs (VA) Medical Center, as appropriate. Written, informed consent was provided by each patient or healthy subject before his or her participation.

The serial CSF sampling studies in PTSD patients were performed in the Psychoneuroendocrinology Research Suite at the Cincinnati VA Medical Center. The lumbar puncture studies of depressed patients were performed at the Clinical Neuroscience Research Center of the Connecticut Mental Health Center, New Haven, and in the Mood Disorders Clinic at Butler Hospital. All CSF samples were assayed for substance P at the Laboratory of Neuropsychopharmacology, Emory University School of Medicine, Atlanta. The PTSD and depression studies were unified when the assay for CSF substance P became available, due to the common interests of the authors of this article.

Patients

PTSD patients and matched healthy volunteers. Eight male combat veterans with chronic PTSD (mean age=42.6 years, SD=7.4) and six healthy comparison subjects (mean age=40.7 years, SD=9.6 years) underwent continuous CSF withdrawal, as previously described (28), from 11:00 a.m. to 5:00 p.m. Substance P concentrations were measured in samples collected at hourly intervals. All patients and healthy volunteers were medication free. In patients who had received psychotropic medication, the medication had been discontinued for a minimum of five drug dis-

appearance half-lives. Healthy subjects were without personal psychiatric history of any DSM-IV axis I condition. The mean Clinician-Administered PTSD Scale (29) score of the veterans with PTSD was 81 (SD=28). All participants had normal platelet counts, clotting times, hematocrit values, hepatic indices, and serum creatinine, pituitary-thyroid axis hormone, and random glucose concentrations.

PTSD patients in the symptom-provocation study. Seven male Vietnam veterans (mean age=51 years, SD=3, range=49–56) with combat-related, chronic PTSD each completed two 6-hour continuous CSF sampling procedures on separate days 6–9 weeks apart (except for one patient, for whom the interval between procedures was 5 months). The patients' mean body mass indexes were 31.0 (SD=6.6) and 31.1 (SD=6.4) before the traumatic and neutral videotape sessions, respectively. The patients had no comorbid medical conditions.

All patients met the DSM-IV diagnostic criteria for PTSD, had had extensive combat experience during the Vietnam War while serving in either the Marines (four subjects) or the Army (three subjects), and had witnessed or participated in atrocities. Their mean Clinician-Administered PTSD Scale score was 78 (SD=24) and their mean Mississippi PTSD Scale (30) score was 155 (SD=18). These scores are collectively indicative of severe PTSD symptoms. Two patients had received comorbid clinical diagnoses of major depression, whereas all others had mild to moderate depressive symptoms. The mean Hamilton Depression Rating Scale (HAM-D) (31) score the day before each CSF sampling session was 13 (SD=8).

Six of the seven subjects had a history of alcohol dependence or abuse, but all six had been abstinent from alcohol for an average of 45 months (range=5 to 216 months). Six of the seven subjects also had histories of abuse of other substances, but their histories indicated that this abuse had ceased a minimum of 3 months before they started the study protocol (two subjects claimed to have abused substances only while serving in Vietnam). A history of alcohol dependence or abuse in a first-degree relative was reported by five of the six patients with knowledge of their relatives (the seventh patient was adopted). The results of urine drug screens were negative in all enrolled patients. Two of the patients smoked tobacco and were nicotine dependent at the time of study; two others were former smokers.

All subjects were medication free for a minimum of more than five medication disappearance half-lives before undergoing CSF sampling. The results of screening laboratory tests performed the evening before the film sessions indicated that all participants were euthyroid. All patients had normal platelet counts, clotting times, hematocrit values, hepatic indices, and serum creatinine, pituitary-thyroid hormone, and random glucose concentrations.

Depressed patients and matched healthy volunteers.

Forty adult outpatients (mean age=36.7 years, SD=13.8, range=18–66) who fulfilled the DSM-IV criteria for unipolar major depressive disorder and 47 healthy comparison subjects (mean age=32.7 years, SD=10.9, range=19–58) were included in the study. Fifty percent (N=20) of the depressed patients and 55% (N=26) of the healthy subjects were female. All enrolled patients had HAM-D scores greater than 17. Semistructured diagnostic interviews were used to determine the presence of unipolar major depressive disorder in the patients and the absence of any current and lifetime DSM-IV axis I disorder in the healthy volunteers. Patients with any other major axis I comorbidity were excluded. Also excluded were subjects with any clinically significant medical disorder detected by means of a medical history, physical examination, and laboratory studies. All subjects were medication free for at least 2 weeks by the time of participation (at least 5 weeks for patients who had been taking fluoxetine).

Procedures

Serial CSF sampling. For both continuous CSF sampling studies, the patients and healthy volunteers were admitted to the Clinical Psychobiology Unit of the Cincinnati VA Medical Center the day before each procedure. During the afternoon, standardized tests were administered. At 8:00 p.m., the subjects ate a standard 665-calorie meal (20% protein, 24% fat, and 56% carbohydrate) and fasted thereafter, with the exception of water ingestion, until the end of the CSF sampling period at 5:00 p.m. the next day. At 8:00 p.m. the evening before the study, an intravenous line was placed in an arm for continuous infusion of normal saline. At midnight, all subjects were confined to bedrest, and, for participants who smoked, no further smoking was permitted until the end of the experiment.

The next morning, at approximately 8:30 a.m. by using strict sterile technique and 1% intradermal and subcutaneous xylocaine anesthesia, a 20-gauge polyamide catheter was placed in the subarachnoid space (spinal canal) by means of a 17-gauge Tuohy needle inserted through the L3–L4 vertebral interspace. The subarachnoid catheter was capped until 11:00 a.m., at which time continuous CSF withdrawal at a rate of 0.1 ml/minute commenced by means of a peristaltic pump. With subjects supine, CSF was collected hourly (until 5:00 p.m.) into iced test tubes for determination of substance P concentrations; these samples were “flash frozen” on dry ice at bedside then kept at -80°C until assayed. Physiological saline solution was infused at a rate of 100 ml/hour throughout each procedure to maintain hydration.

Lumbar punctures. Subjects with major depression and matched healthy volunteers underwent a single lumbar puncture procedure, standardized to yield CSF samples at 12:00 noon \pm 15 minutes, as outpatients at either the Clinical Neuroscience Research Unit at Connecticut Mental Health Center or the Mood Disorders Research Program at Butler Hospital. All subjects agreed to comply with instructions for a modified diet and activity schedule in the 24 hours preceding the lumbar puncture. Samples were collected with subjects seated in a forward-leaning position. After intradermal injection of 1% lidocaine, a 20-gauge introducer needle was used to penetrate the skin and superficial tissue. The introducer was used because the Sprotte 24-gauge pencil point spinal needle (B. Braun Medical, Bethlehem, Pa.) is very thin and has a relatively dull tip. The spinal needle was then inserted, by means of the introducer, through the L3–L4 or L4–L5 interspace into the spinal canal. A total of 12 cm³ of CSF was collected, immediately divided into 0.5-ml aliquots, and frozen at -80°C until assayed.

Use of videotapes for symptom provocation in PTSD. To examine the effects of symptom provocation on CSF substance P concentrations in patients with PTSD, at 12:00 noon, 1 hour after the start of serial CSF sampling in the second CSF sampling procedure, either a “stress” or neutral videotape was shown at moderately high volume in a random order of assignment. Both the stress and neutral videotapes were 60 minutes in duration. The stress videotape consisted of a 15-minute training film compiled for medics awaiting deployment to Vietnam (provided by Barbara Rounds-Kugler, R.N., a research nurse and decorated Vietnam veteran; the film itself was untitled and without attribution) followed by 45 minutes of the documentary film *Letters Home from Vietnam* (Home Box Office Studios, 1987). The medic training tape was by far the most graphic and disturbing portion of the stressful film. This tape consisted of serial scenes, with sound but no voice-over or music, of combat and combat casualties both on the battlefield and in a field hospital. It included depictions of several helicopter landings and take-offs, firefights (gun battles), artillery and mortar firing, shots of incoming artillery and mortar rounds, and infantry charges, including one in which an underground enemy tunnel was overrun. Multiple bloody and moaning

soldiers were shown. The neutral videotape consisted of an oil painting instructional film.

Vital sign and mood assessment during serial CSF sampling. Mood and anxiety were self-rated with 100-mm visual analogue scales at 10-minute intervals throughout each procedure (32). The analogue scale anchors were “high” and “low.” An automated vital signs monitor (Dinamap, Critikon, L.L.C., Tampa, Fla.) was used to monitor heart rate and blood pressure from the left leg at hourly intervals.

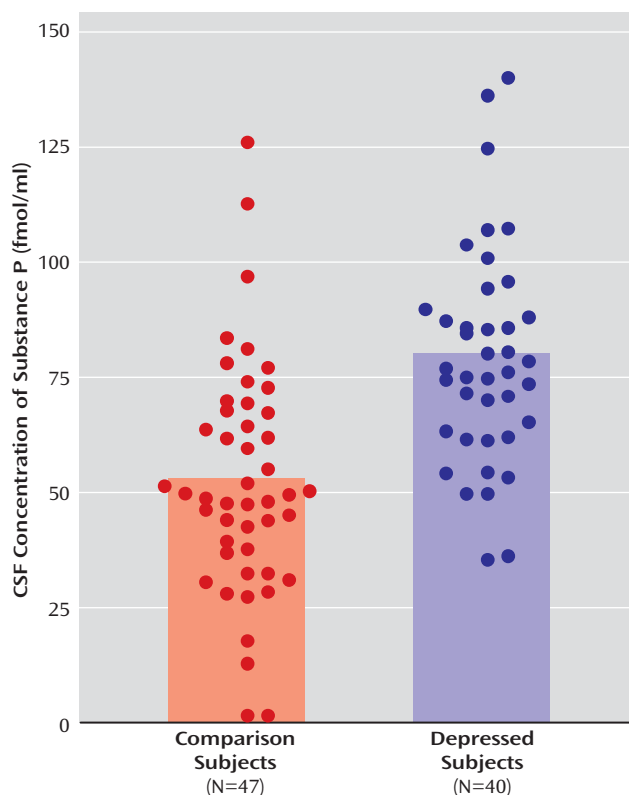
CSF substance P assay. CSF substance P immunoreactivity was determined with solid phase radioimmunoassay in CSF samples by using a highly specific substance P antibody. The researchers who conducted the assay were blinded to the identity of the groups from which the CSF samples were obtained. Briefly, Nunc-Immuno module plates (Fisher Scientific, Hamilton, N.H.) were incubated for 1 hour at room temperature with 250 ng/well of protein G in a 0.1-M sodium bicarbonate solution with a pH of 9.0. The plates were rinsed three times in wash buffer (150 mM of K^2HPO_4 , 20 mM of NaH_2PO_4 , 200 mM of ascorbic acid, 0.2% polysorbate 20, 0.1% sodium azide) with a pH of 7.6. One hundred microliters of substance P antibody (#RAS-7415, 500-reaction lyophilized formulation [Bachem, King of Prussia, Pa.] reconstituted in 60 ml of wash buffer containing 0.1% gelatin) was added to each well, and the plates were incubated at room temperature for 2 hours. The antibody solution was aspirated, and the samples and standards were added to the wells in a volume of 50 μl . Labeled ^{125}I -substance P (#H-5104, Bachem, King of Prussia, Pa.) was diluted to approximately 7000 counts per minute/25 μl wash buffer, and 25 μl was added to each well. Nonspecific binding was determined in wells containing only protein G (no antibody). Plates were incubated at 4°C for 24 hours. After this period, the wells were aspirated, separated, placed in 12 \times 75-mm borosilicate glass tubes, and counted on a four-channel gamma counter. The sensitivity of the assay was 1.5 fmol/ml. Intra-assay variability was 8.2%, and interassay variability was 9.7%.

Statistical Analysis

Baseline serial CSF sampling in PTSD patients and healthy volunteers. Substance P concentrations in the patients with PTSD and healthy volunteers were compared by using repeated-measures analysis-of-variance (ANOVA) with the independent variables of group and time. All p values quoted are for a two-sided hypothesis test; p values <0.05 were considered significant for these and all other results.

Symptom provocation in PTSD. In the symptom-provocation study, the following variables were measured for each patient: substance P concentration, heart rate, systolic blood pressure, diastolic blood pressure, and anxiety and mood self-ratings. Each measurement was taken 50 minutes before the subject viewed each videotape (baseline) and at the following six time points: 10, 70, 130, 190, 250, and 310 minutes after the start of the videotape. The percentage change from baseline was computed for each subject and film at each time point by using the following formula: $([\text{measurement at time point}] - \text{baseline}) / \text{baseline} \times 100\%$. Last, the difference in percentage change from baseline was calculated for each subject at each time point for each of the two films. This difference (Δ percentage change from baseline) was equal to the percentage change from baseline during the provocative film minus the percentage change from baseline during the neutral film. For example, if a patient had a heart rate of 75 bpm at baseline and a heart rate of 80 bpm at 130 minutes while viewing the neutral film, that patient's percentage change from baseline for heart rate for the neutral film at 130 minutes would be calculated as follows: $(80 - 75) / 75 \times 100\% = 6.7\%$. If the patient had heart rates of 77 bpm and 92 bpm at baseline and 130 minutes, respectively, for the provocative film, the patient's percentage

FIGURE 1. CSF Concentrations of Substance P in Depressed Patients and Healthy Comparison Subjects^a



^a Bars extend to the mean values. A significant between-group difference in mean values was found ($p < 0.0001$, ANOVA).

change from baseline for heart rate for the provocative film at 130 minutes would be calculated as follows: $(92 - 77) / 77 \times 100\% = 19.5\%$. The measure of interest is the difference between these two values—the patient's Δ percentage change from baseline for heart rate at 130 minutes (19.5% minus 6.7% = 12.8%). If there is no effect due to the provocative film, these values should be approximately zero on average. For the vital signs and mood self-ratings, the Δ percentage change from baseline was tested for statistical significance versus zero at each of the six time points. Paired t tests were used to conduct these hypothesis tests. If the data appeared nonnormal (Shapiro-Wilk test p value < 0.20), then the Wilcoxon signed-ranks test was used.

Comparison of depressed patients and healthy volunteers. Pearson's product-moment correlations were generated to examine the relationships between CSF substance P concentration, subject age, and CSF specimen storage time in the freezer. CSF substance P concentrations were not significantly correlated with age when the data for healthy comparison subjects and depressed patients were examined separately. However, when a large database of CSF substance P concentrations in patients with mood disorders was explored (unpublished 2004 data of L. Carpenter; available from the author on request), a significant negative correlation was found between age and substance P level ($N = 113$; $r = -0.23$, $p = 0.01$). Therefore, ANOVA with age as a covariate was used to determine the effect of subject group on CSF substance P concentration. T tests and chi-square tests were used to compare the groups with regard to mean age and gender composition, respectively.

Results

CSF Substance P Concentration in Major Depression

CSF concentrations of substance P were significantly higher in patients with major depression, compared with healthy subjects, after adjustment for age effects ($F = 25.5$, $df = 1, 84$, $p < 0.0001$) (Figure 1). The mean CSF substance P concentration was 51% higher in the depressed group (mean = 79.1 fmol/ml, $SD = 23.5$) than in the healthy comparison group (mean = 52.5 fmol/ml, $SD = 25.1$).

Serially Sampled CSF Substance P in PTSD at Baseline

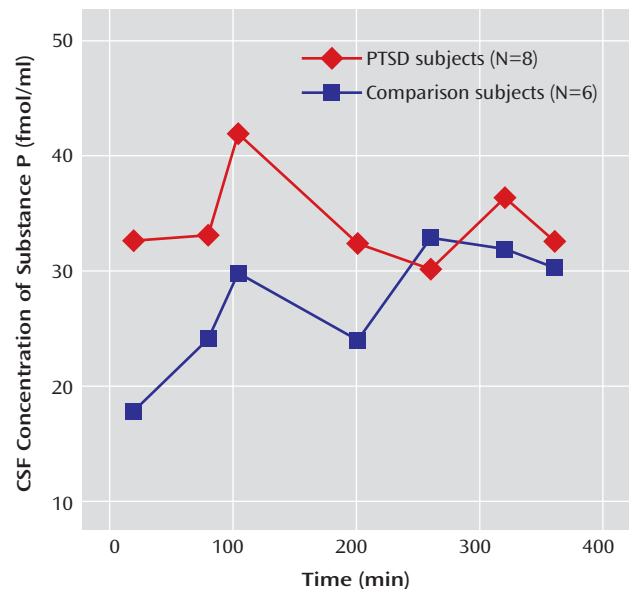
As determined by serial sampling through an indwelling spinal canal catheter, mean CSF substance P concentrations were significantly higher in the patients with PTSD (mean = 34.5 fmol/ml, $SD = 4.8$) than in the healthy comparison subjects (mean = 22.2 fmol/ml, $SD = 2.8$) ($F = 6.55$, $df = 1, 12$, $p < 0.03$) (Figure 2). Analysis of these data also revealed a time effect of 0.025 that approached significance ($F = 3.44$, $df = 1, 66$, $p = 0.07$). This result may be interpreted as an overall slope (i.e., substance P levels increased slightly for both groups during the study). However, there was no statistically significant interaction between group and time (i.e., the increase in substance P over time was the same for the two groups) ($F = 2.37$, $df = 1, 66$, $p = 0.13$).

Effect of Symptom Provocation in PTSD

During the 1-hour traumatic videotape, the maximum change in subjective anxiety ratings between any two adjacent points was on average 15.3 mm higher than during the neutral videotape (signed rank = 14, $p < 0.02$, two-sided, Wilcoxon signed-ranks test). The percentage change from baseline in mood was significantly greater during the traumatic movie than during the neutral film at both 10 minutes (Δ percentage change from baseline = -42.8%; $t = -2.54$, $df = 6$, $p < 0.05$) and 70 minutes (Δ percentage change from baseline = -57.4%; $t = -3.06$, $df = 6$, $p < 0.05$).

In the within-subject, crossover serial CSF sampling study (symptom-provoking versus neutral stimulus), hourly substance P concentrations were determined at baseline (-50 minutes before commencement of the audiovisual stimulus) and at 10, 70, 130, 190, 250, and 310 minutes after commencement of the audiovisual stimulus. CSF substance P concentrations increased by 169% and 90.6% of baseline levels at 10 and 70 minutes, respectively, after the start of the traumatic videotape, but changed by only 1.1% and -8.1% of baseline levels 10 and 70 minutes after the start of the neutral videotape (signed rank = 12, $p < 0.05$ at 10 minutes and $t = 3.05$, $df = 6$, $p < 0.03$ at 70 minutes for the neutral versus the traumatic videotape [note that the Shapiro-Wilk p value equals 0.87 for substance P levels at 70 minutes, indicating that the data appear Gaussian; using the Wilcoxon nonparametric test, signed rank = 11, $p < 0.07$]) (Figure 3). Remarkably, 250 and

FIGURE 2. Serial CSF Concentrations of Substance P in Vietnam Combat Veterans With Chronic PTSD and Matched Healthy Comparison Subjects^a



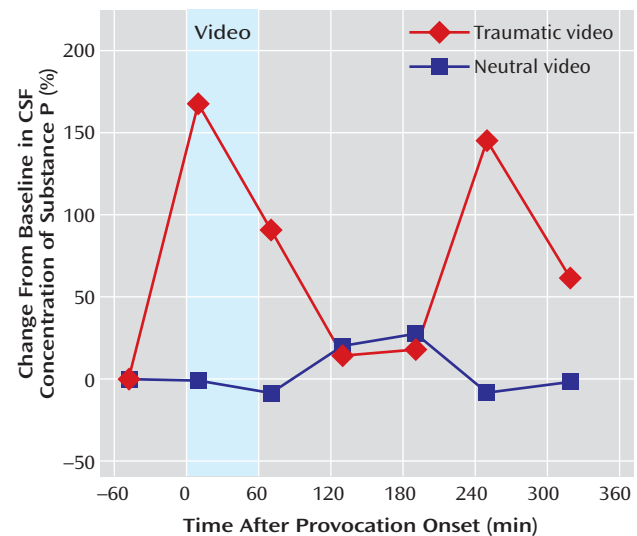
^a CSF sampling commenced 3 hours after placement of a flexible polyamide subarachnoid catheter in the spinal canal. Mean CSF substance P concentrations were significantly greater in the patients with PTSD than in the comparison subjects ($p < 0.03$, ANOVA).

310 minutes after the start of the traumatic film, CSF substance P concentrations remained elevated by 146% and 60.7%, respectively, above the premovie baseline, whereas 250 and 310 minutes after the start of the neutral movie, levels were 8% and 2%, respectively, lower than baseline (signed rank=13, $p = 0.03$ at 250 minutes and signed rank=11, $p < 0.08$ at 310 minutes for neutral versus traumatic videotape) (Figure 3). However, the increase in CSF substance P concentrations that followed the traumatic stimuli appeared to be biphasic (Figure 3), as the levels at 130 and 190 minutes were similar to those obtained after the neutral stimuli. Systolic blood pressure increased significantly more from baseline during exposure to the traumatic film, compared with the neutral film, at 10 minutes (14.2% greater increase from baseline during exposure to the traumatic videotape, relative to the neutral videotape, $t = 3.85$, $df = 6$, $p < 0.02$) and at 70 minutes (22.1% greater increase during exposure to the traumatic videotape, relative to the neutral videotape, $t = 9.02$, $df = 6$, $p < 0.001$).

Discussion

The current data, not only demonstrate significantly elevated CSF substance P concentrations in patients with major depression but also demonstrate elevated CSF substance P concentrations in patients with PTSD. Moreover, in patients with PTSD who each underwent continuous CSF sampling on two occasions, we observed a marked increase in CSF substance P concentrations during and after

FIGURE 3. Serial CSF Substance P Concentrations in Vietnam Combat Veterans With PTSD Before, During, and After a 60-Minute Traumatic or Neutral Videotape Stimulus^a



^a The videotape stimulus was begun at time 0. CSF substance P concentrations were determined 50 minutes before commencement of the videotape and 10, 70, 130, 190, 250, and 310 minutes after commencement. A within-subject crossover design was used. The traumatic stimulus consisted of a 60-minute videotape showing scenes of combat or related scenes from the Vietnam conflict; the neutral stimulus consisted of a 60-minute instructional videotape on oil painting. CSF substance P concentrations rose significantly after exposure to the traumatic stimulus but not after exposure to the neutral film.

a blood pressure-elevating, anxiogenic, mood-lowering stimulus but not after a neutral stimulus, implicating CNS release of substance P in the mechanism of acute PTSD symptoms.

Taken together, the current results suggest a pathophysiological role for tonically excessive substance P release in major depression and PTSD and, moreover, indicate that CNS substance P is robustly secreted in response to acute psychological stress.

It is of interest that CSF substance P concentrations were higher—about twice as high—in the subjects and patients in whom CSF was obtained immediately after lumbar puncture than in those from whom CSF was obtained by serial sampling by means of a polyamide subarachnoid catheter that had remained in place for approximately 3 hours before CSF collection began. Lumbar puncture and its anticipation are, to varying degrees, stressful experiences, and we have demonstrated in these studies that substance P levels increase in association with stressful psychological stimuli. Therefore, it is likely that the higher substance P concentrations in CSF samples obtained immediately after lumbar puncture are stress-related phenomena. However, we did not assess the study subjects' level of anxiety in response to the procedure itself. Alternatively, we cannot rule out nonspecific binding of substance P to the polyamide subarachnoid catheter as an ex-

planation for the lower levels in subjects and patients who underwent serial CSF sampling. However, the CSF substance P concentrations obtained by means of the polyamide catheters were in the same range as those previously reported by other investigators (33). In any event, identical methods were used to study patients and comparison subjects in each situation in which statistical comparisons were made. Nevertheless, it will be important to identify and characterize other factors (besides acute stress and a diagnosis of depression or PTSD) that regulate CSF substance P concentration.

Other preexisting basic and clinical findings are consistent with the elevations in CSF substance P reported here in the patients with PTSD. For example, intrathecal administration of substance P to anesthetized rats has been shown to induce an increased heart rate that is blocked by the β -adrenergic antagonist propranolol (34). Propranolol has been shown to be effective in preventing the development of PTSD and ameliorating PTSD symptoms (35, 36). In addition, various inflammatory cytokines have been shown to stimulate release of substance P (37), and elevated concentrations of the proinflammatory cytokine interleukin-6 have been reported in postcombat PTSD patients (38) and in depressed patients (39).

In summary, the present data demonstrate elevated substance P concentrations in the CNS of depressed patients and patients with PTSD. Moreover, our investigations reveal that CSF substance P levels in PTSD patients markedly increase during exposure to traumatic psychological stimuli but not during exposure to neutral psychological stimuli. These data provide the pathophysiological rationale for initiation of clinical trials of substance P antagonists in PTSD. More generally, our observations show that traumatic psychological stimuli can rapidly elicit robust changes in the concentrations of a peptide in the CSF in humans.

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