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ELEVATED CEREBROSPINAL FLUID LEVELS OF SUBSTANCE P IN PATIENTS WITH THE FIBROMYALGIA SYNDROME

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Objective. **To measure, and seek clinical correlates with, levels of substance P (SP) in the cerebrospinal fluid (CSF) of fibromyalgia syndrome (FMS) patients.**

Methods. **CSF from 32 FMS patients and 30 normal control subjects was tested for SP by radioimmunoassay. Clinical measures included tender point examination and standardized questionnaires.**

Results. **CSF SP levels were 3-fold higher in FMS patients than in normal controls ($P < 0.001$), but they correlated only weakly with tenderness found on examination.**

Conclusion. **SP is significantly elevated in FMS CSF, but other abnormalities must exist in FMS to more fully explain the symptoms.**

Fibromyalgia syndrome (FMS) is a chronic, painful, musculoskeletal disorder commonly seen in rheumatology practice (1–4). Prevalence studies in Norway, Denmark, Germany, and South Africa have shown that 3–10% of the general population is affected, which would make FMS more common than rheumatoid arthritis (5). The comparison with rheumatoid arthritis is pertinent because the severity of the discomfort experienced among the 2 patient groups is comparable (6,7). In addition, their ability to perform specific work tasks is similarly impaired (7). Most FMS patients report having insomnia and exhibit nonrestorative sleep on polysomnographic recordings (8,9).

No consistent histologic abnormality has been identified in the tender muscles of FMS patients (10), so their pain may result from something other than peripheral tissue injury. The discomfort of FMS could result from aberrant central nervous system perception of normal stimuli (allodynia). The application of that concept to chronic musculoskeletal pain is not new (11,12), but it may be critical to understanding the pathogenesis of FMS (13).

Substance P (SP) is an 11-amino acid peptide which has a role in the neurotransmission of pain from the periphery to the central nervous system. In one study, the serum concentration of SP in FMS patients did not differ from that in controls (14). In contrast, Vaeroy et al (15) reported elevated levels of SP in cerebrospinal fluids (CSF) obtained from FMS patients (16,17).

The physiologic functions of SP are influenced by serotonin (18), which is a recognized chemical mediator of deep sleep and pain perception (19). Several years ago, Moldofsky and Warsh (20) suggested that a serotonin deficiency may occur in FMS, and investigators have recently observed such a deficiency in FMS sera (21–23).

The present study was undertaken to measure the concentration of SP in CSF obtained from clinically characterized FMS patients and concurrently studied normal control subjects. A second objective was to seek clinical correlates of SP among validated measures of FMS severity.

PATIENTS AND METHODS

Subjects. Sequential FMS patients who were ≥18 years of age, not selected for sex or ethnic origin, were

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identified from the academic rheumatology practice of one of the authors (IJR). They were invited to participate in the study if they met the American College of Rheumatology criteria for primary FMS (24) and were willing to undergo a lumbar puncture for research purposes. Potential study subjects were informed regarding the study goals and risks, under the auspices of the Institutional Review Board of The University of Texas Health Science Center at San Antonio.

Normal controls were prospectively sought from among patients' relatives, acquaintances, and other area residents, with the goal of matching the patients with respect to age, sex, and ethnic origin (Caucasian versus Hispanic [Mexican-American]). The controls were not required to be free of musculoskeletal pain symptoms, provided that any discomfort experienced was considered by them to be trivial, that they had not sought medical care because of pain during the previous 5 years, and that they failed to meet criteria for FMS (24). Each subject gave informed consent and received a financial stipend.

Clinical measures. Comprehensive clinical assessments were performed by self-administered questionnaires and by physical examination on the day of the subject's lumbar puncture. Medical history-taking and examination sought confirmation of the subject's diagnosis and any contraindication to performance of a lumbar puncture. All evaluations and lumbar puncture procedures were performed in the morning (25).

Separate visual analog scales (VAS; 10-cm horizontal) were used to document perceived somatic pain level, morning stiffness severity, sleep quality, and physical functional ability (25). Functional status was also assessed by the Stanford Health Assessment Questionnaire (HAQ) (7,25,26). Evidence for depression was sought using the Center for Epidemiological Studies Depression (CES-D) Scale (27) and the Zung Depression Scale (28). The level of situational frustration was assessed with the Hassles Scale (29), which was previously reported to be useful in the study of FMS (30).

Medications ingested during the 2 weeks prior to the lumbar puncture procedure were documented. Subjects were required to discontinue all psychotropic, analgesic, and catecholamine-blocking medications for 2 weeks prior to the lumbar puncture. Acetaminophen (up to 650 mg every 4 hours) was allowed, if needed, as a pain medication until 48 hours prior to the lumbar puncture. The tender point examination was performed on all subjects by a single examiner (IJR). The severity of discomfort induced by 4 kg of digital palpation pressure at each of 18 typical tender points (24,31) was used to calculate the tender point index (TPI) (25). A dolorimeter (Pain Diagnostics & Thermography, Great Neck, NY) with a 0.95-cm^2 contact surface (32,33) was pressed against each of the same tender points to determine the pain threshold (in kg) at each site. The average pain threshold (TPA) was then defined as the average threshold value for all 18 tender point sites (25).

Collection of CSF. CSF (12 cc) was collected from seated subjects by lumbar puncture at the L4–L5 interspace, using a 22-gauge Whitacre pencil tip, side vent spinal needle (Becton Dickinson, Great Neck, NY). The subjects then lay recumbent for 2 hours. Each CSF sample was quickly divided into 2 fractions and centrifuged at 4°C for 10 minutes at 1,000*g* to remove any cells. The rapid cooling was intended to avoid in vitro alteration of SP^{1-11} by converting enzymes (34). After centrifugation, 2-ml fractions were aliquoted into plastic cryogenic tubes and stored frozen at −70°C.

Laboratory measures. CSF analysis was performed on numbered samples by a technician who was blinded to their source. SP was extracted from CSF by a method similar to that described by Vaeroy et al (15). Briefly, Sep Pak C-18 cartridges (Water Associates, Milford, MA) were sequentially washed with 5 ml 100% methanol, 5 ml of 0.1*M* HCl–0.1% trifluoroacetic acid (TFA), 5 ml methanol, and 10 ml deionized water. A 2-ml CSF sample from each subject was thawed in cold water and its peptide contents immediately adsorbed on a cartridge column. After washing the columns with 10 ml deionized water, the peptide was eluted with 3 ml 0.1% TFA in methanol–0.1*M* HCl and dried in a stream of dry nitrogen.

Extracted samples were analyzed in duplicate. Two hundred microliters of synthetic (Tyr^8) SP (INCSTAR, Stillwater, MN) in concentrations ranging from 5 pg/ml to 625 pg/ml provided the standard curve. Samples were diluted in 500 μl bovine serum albumin–peptone buffer, and 200 μl was placed in each 12 ×75-mm glass culture tube. Rabbit anti-human SP serum (cross-reactivity with enkephalins <0.002%, β-endorphin <0.008%, eledoisin <0.002%, physalaemin <0.002%) and ^{125}I-labeled intact synthetic (Tyr^8) SP (1,250 pg/ml/μCi), each in 100 μl of buffer, were mixed with the test sample and stored overnight at 4°C. Incubation was terminated by addition of 100 μl rabbit gamma globulin carrier and 500 μl of saturated ammonium sulfate. The tubes were incubated at 25°C for 25 minutes, followed by centrifugation (10 minutes at 760*g*) and decanting of the supernatants. Radioactivity in the pellet was measured in a gamma counter (Packard Instruments, Downers Grove, IL), and SP content was determined by comparison with the standard curve. The agreement of measured standards with the predicted recovery was 95–98%.

Statistical analysis. Sample size determinations were based on the results of a prior study (15) in which the mean CSF SP level in 35 healthy volunteers was 9.6 fmoles/ml (SD 18.9) and the mean in 30 FMS patients was 36.1 fmoles/ml (SD 14.7), giving an effect size of 1.55. The sample size per group that would be required in order to detect a more conservative effect size (only half as great [0.78]) was determined by assuming a 2-sided *t*-test and a 5% level of significance (35). Thus, it was predicted that a sample size of 25 subjects in each group would provide a power of 76%, but a larger sample size (30 per group, power = 83%) was chosen in order to increase the chance of detecting correlations of SP with clinical variables.

Statistical analysis was accomplished using the PRODAS analytic system for microcomputers (Conceptual Software, Houston, TX). Continuous variables were analyzed by *t*-tests and regression models. The Pearson product-moment correlation and linear models were used to compare SP concentrations with 3 primary clinical variables (TPI, TPA, VAS pain) and 4 secondary clinical variables (HAQ, CES-D, Hassle Scale, VAS stiffness). Group differences (FMS versus normal controls) were assessed by linear regression modeling controlled for age, ethnic background, and sex. The null hypothesis predicted no group difference in SP

Table 1. Characteristics of the study subjects, by group*

Variable	Controls	Fibromyalgia patients	*P*
n	30	32	
Age, years	36.6 ± 11.2	49.6 ± 9.4	<0.001
Sex, no. (%) female	17 (56.7)	26 (86.7)	0.04
Ethnic background, Caucasian/Hispanic	15/15	13/19	0.46
Pain, cm†	0.1 ± 0.6	7.8 ± 1.9	<0.001
Stiffness, cm†	0.6 ± 1.2	7.8 ± 2.4	<0.001
Anxiety, cm†	1.5 ± 2.6	7.0 ± 3.2	<0.001
Depression, cm†	0.8 ± 1.6	5.8 ± 3.1	<0.001
Physical function, HAQ	0.4 ± 0.5	1.6 ± 0.6	<0.001
Tender point index	1.1 ± 4.5	34.5 ± 12.0	<0.001
Pain threshold, kg	7.4 ± 2.2	3.0 ± 1.3	<0.001
CES-D Scale	7.6 ± 7.4	27.1 ± 12.5	<0.001
Zung Depression Scale	0.4 ± 0.09	0.6 ± 0.11	<0.001
Hassles Scale	56.5 ± 58.6	94.1 ± 67.7	0.02

* Except where otherwise indicated, values are the mean ± SD. HAQ = Health Assessment Questionnaire; CES-D Scale = Center for Epidemiological Studies Depression Scale.
† Ten-centimeter visual analog scale.

concentration and no correlation of SP with any clinical measure of FMS severity.

RESULTS

Subject characteristics. Thirty-two patients with FMS and 30 normal controls were enrolled over an 18-month period. One FMS patient was hypertensive, 1 had a positive antinuclear antibody test result but did not meet criteria for any other rheumatic disease, 1 also had a diagnosis of myofascial pain dysfunction syndrome (36), 1 was hypermobile (37,38), and 2 had previously been clinically depressed. One normal control subject was reported to have had "hepatitis" years earlier.

Table 1 presents a demographic and clinical comparison of the 2 groups. They were significantly different with respect to 2 key demographic variables (age and sex), because it proved to be quite difficult to recruit fully matched control subjects who were willing to undergo a lumbar puncture. The other observed differences represent characteristic findings in FMS (1,25). The mean HAQ score of 1.6 among FMS patients indicated substantial physical dysfunction (39,40).

Lumbar puncture complications. The lumbar punctures were initially performed using a Becton Dickinson 22-gauge Quinke spinal needle, with which the frequency of spinal headache was 18%. When the Becton Dickinson 22-gauge Whitacre pencil-tip, side-vent spinal needle became available, it was used and was credited with a drop in the spinal headache rate to <4%. The only other problem observed by ~10% of subjects was minor local back discomfort at the lumbar puncture site, lasting 1–3 days.

Table 2. Cerebrospinal fluid substance P concentrations, by group

Group (n)	Substance P concentration, fmoles/ml		
	Minimum	Maximum	Mean ± SD
FMS (32)*	12	68	42.8 ± 14.9†
Control (30)	5	26	16.3 ± 6.0

* FMS = fibromyalgia syndrome.
† $P < 0.001$ versus control group.

CSF SP. Measurements of SP in the CSF samples disclosed a significantly higher average level in the FMS patients than in the normal controls. Table 2 shows these results. The findings in individual subjects are illustrated in Figure 1.

Demographic correlates. Regression models were developed to assess the significance of the group

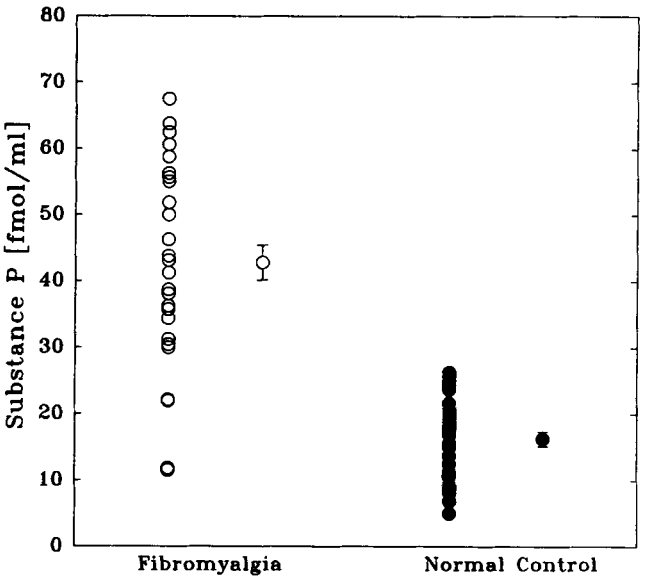

Figure 1. Substance P concentrations in cerebrospinal fluid samples from fibromyalgia syndrome patients and normal controls. Each dot represents an individual patient; dots with bars represent the mean ± SEM for each group. There was very little overlap of values between the 2 groups, and the means were significantly different ($P < 0.001$).

Table 3. Regression models of cerebrospinal fluid substance P concentration by group, with adjustment for age, ethnicity, and sex*

Source	df	F	*P*	R^2
Full regression model				
Group	1	5.1	0.03	0.66
Age	1	0.9	0.35	
Ethnicity	1	6.8	0.01	
Sex	1	0.6	0.44	
Group by age	1	0.04	0.85	
Group by ethnicity	1	1.9	0.17	
Group by sex	1	2.0	0.16	
Best reduced regression model				
Group	1	93.3	<0.001	0.62
Ethnicity	1	6.7	0.01	

* Group = fibromyalgia syndrome or control; df = degrees of freedom.

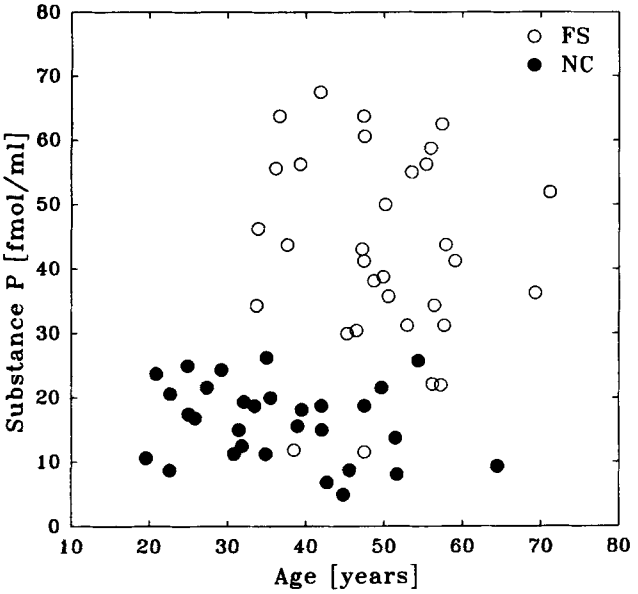

Figure 2. Substance P concentrations in cerebrospinal fluid samples from fibromyalgia syndrome patients (FS) and normal controls (NC), by age of the subjects. Fibromyalgia patients generally exhibited higher values than did normal controls. Only 4 (12.5%) of the fibromyalgia patients' values fell within the range of the normal controls. The distribution of values failed to exhibit any relationship to age in either group.

difference in CSF SP levels after adjustment for age, ethnic background, and sex. The full model and the best reduced model are summarized in Table 3. Age and sex did not contribute significantly after adjustment for ethnicity. The group mean values for CSF SP remained significantly different even after adjustment for ethnicity ($P < 0.001$). The 95% confidence interval for the mean difference (FMS patients minus normal controls) was 21.4–32.9 fmoles/ml.

CSF SP concentrations appeared to be influenced by ethnicity, but not by sex. Table 4 shows that Caucasian subjects exhibited higher mean CSF SP levels than did Hispanic subjects ($P = 0.02$), but it must be kept in mind that the FMS and normal control groups in this study did not differ ethnically.

The lack of significant variation in the mean SP difference with age, as noted through regression modeling (Table 3), was of interest since the groups did differ significantly in age. There was no association between CSF SP concentration and age in the FMS group ($P = 0.68$) or in the normal control group ($P = 0.19$). In an analysis of both groups combined, the difference in CSF SP group means did not change significantly with age ($P = 0.97$). Figure 2 illustrates the lack of any relationship between CSF SP and age. With only 4 exceptions (12%), the SP concentrations were higher in FMS patients than in control subjects regardless of age.

Another approach to this question involved creation of a new database by omitting the younger control subjects (age <28 years) and the older FMS patients (age >54 years). There remained 21 FMS patients and 22 controls, of comparable mean age (mean ± SD 44.4 ± 6.3 years and 41.3 ± 9.2 years, respectively; $P = 0.20$). Yet their mean ± SD SP concentrations remained significantly different (43.3 ± 15.7 fmoles/ml versus 15.6 ± 6.1; $P < 0.001$).

Clinical correlates. Table 5 summarizes the correlation between SP and 10 clinical measures in FMS. Borderline significant correlations were observed with TPA ($r = 0.32$, $P = 0.07$) and TPI ($r = -0.30$, $P = 0.10$). The least-squares regression lines and their 95% confidence bands for these comparisons are shown in

Table 4. Relationship of sex and ethnicity to cerebrospinal fluid substance P concentrations in the fibromyalgia syndrome patients

Variable	Number	Substance P*	*P*
Sex			
Female	26	41.3 ± 14.9	0.23
Male	6	49.5 ± 14.6	
Ethnicity			
Caucasian	13	49.9 ± 12.3	0.02
Hispanic	19	37.9 ± 14.9	

* Mean ± SD fmoles/ml.

Table 5. Correlation between cerebrospinal fluid substance P concentrations and clinical variables in the fibromyalgia syndrome patients*

	PAN	STF	HAQ	TPI	TPA	ANX	DEP	CES	ZNG	HAS
SP	−0.09	0.24	−0.12	−0.30†	0.32‡	−0.22	−0.07	0.01	−0.17	0.15
PAN		0.37§	0.02	−0.05	0.13	0.31	0.17	0.09	0.05	0.06
STF			−0.07	−0.11	0.32	0.32	0.12	0.19	0.06	−0.06
HAQ				0.12	−0.21	−0.18	0.10	0.35	0.54§	0.09
TPI					−0.58§	0.17	0.13	0.28	0.26	0.34§
TPA						−0.17	−0.28	−0.24	−0.22	−0.18
ANX							0.39§	0.20	0.05	0.17
DEP								0.62§	0.52§	0.31
CES									0.74§	0.33
ZNG										0.34

* Values are expressed as the Pearson product-moment correlation coefficient (r). The Bonferroni correction for significance, when simultaneously correlating all 3 primary clinical variables (PAN, TPI, TPA) with cerebrospinal fluid substance P concentrations at the $P = 0.05$ level, would be $P = 0.05/3$ or $P < 0.017$, for which $r > 0.42$. PAN = subjective pain by visual analog scale (VAS); STF = morning stiffness by VAS; HAQ = Stanford Health Assessment Questionnaire; TPI = tender point index; TPA = tender point average (average tender point threshold by dolorimeter); ANX = anxiety by VAS; DEP = depression by VAS; CES = depression by Center for Epidemiological Studies Depression questionnaire; ZNG = depression by Zung Scale; HAS = Hassles Scale.
† $P = 0.10$, uncorrected.
‡ $P = 0.07$, uncorrected.
§ $P < 0.05$, uncorrected.

Figure 3. It should be noted that the regressions indicate an inverse relationship between SP levels and tenderness. Among these FMS patients, SP did not correlate with the VAS self-assessment of pain severity or with any other clinical variable.

Several anticipated relationships between clinical variables were found. For example, TPA correlated inversely with TPI ($r = -0.58$, $P = 0.003$); pain severity by VAS with perceived stiffness ($r = 0.37$, $P = 0.04$) but not with depression or anxiety; the 2 formal depression instruments (CES-D and Zung Scale) with each other ($r = 0.74$) and with depression by VAS (CES-D $r = 0.62$, Zung Scale $r = 0.52$). FMS patients reported a level of anxiety (by VAS) which correlated with VAS Depression ($r = 0.39$, $P < 0.05$) but not with the Hassles Scale ($r = 0.17$). Of interest were the correlations between TPI and the Hassles Scale ($r = 0.34$, $P < 0.05$), and between physical dysfunction (HAQ) and depression by the Zung Scale ($r = 0.54$, $P = 0.002$).

There was no significant relationship between SP levels and depression. Assuming that a CES-D score of ≥18 indicates "possible depression" (25,27), 25 of 32 FMS patients (78.1%) and 3 of 30 controls (10%) were affected. When subjects were subgrouped by CES-D values above or below 18, the mean SP values did not differ between the FMS subgroups (mean ± SD 42.7 ± 14.8 fmoles/ml versus 43.2 ± 16.6; $P = 0.93$) or the normal control subgroups (13.8 ± 10.4 versus 16.6 ± 5.6; $P = 0.67$). Finally, a linear regression of SP on group (FMS, normal controls) and CES-D ≥18 (yes, no) revealed no significant interaction.

The data in Figure 4 were obtained when SP concentrations were examined for normality. FMS patients appeared to fall into 2 subgroups with respect to CSF SP levels: those with levels in the 30–45 fmole/ml range and those with levels in the 55–65 fmole/ml range. For this reason, clinical data on the 20 FMS patients with SP levels in the 10–50-fmole/ml range were compared with data on the 12 whose levels were in the 50–70-fmole/ml range. These subgroups were not significantly different with respect to age (mean ± SD 49.7 ± 9.1 years versus 49.4 ± 10.2, respectively), sex (% female = 85% versus 75%), or ethnicity (% Caucasian = 30% versus 58%). They had similar values for TPI (34.7 versus 34.3), TPA (2.7 versus 3.4), pain (7.8 versus 7.8), anxiety (7.7 versus 5.7), depression (6.0 versus 5.5), and HAQ (1.6 versus 1.6). Only the difference in stiffness by VAS (mean ± SD 7.3 ± 0.6 in the lower-SP-concentration subgroup versus 8.6 ± 0.5 in the higher-SP-concentration subgroup; $P = 0.08$) even approached significance.

DISCUSSION

SP levels are normally high in the axons of primary unmyelinated C-fiber sensory neurons (41). When depolarized by a noxious stimulus, these fi-

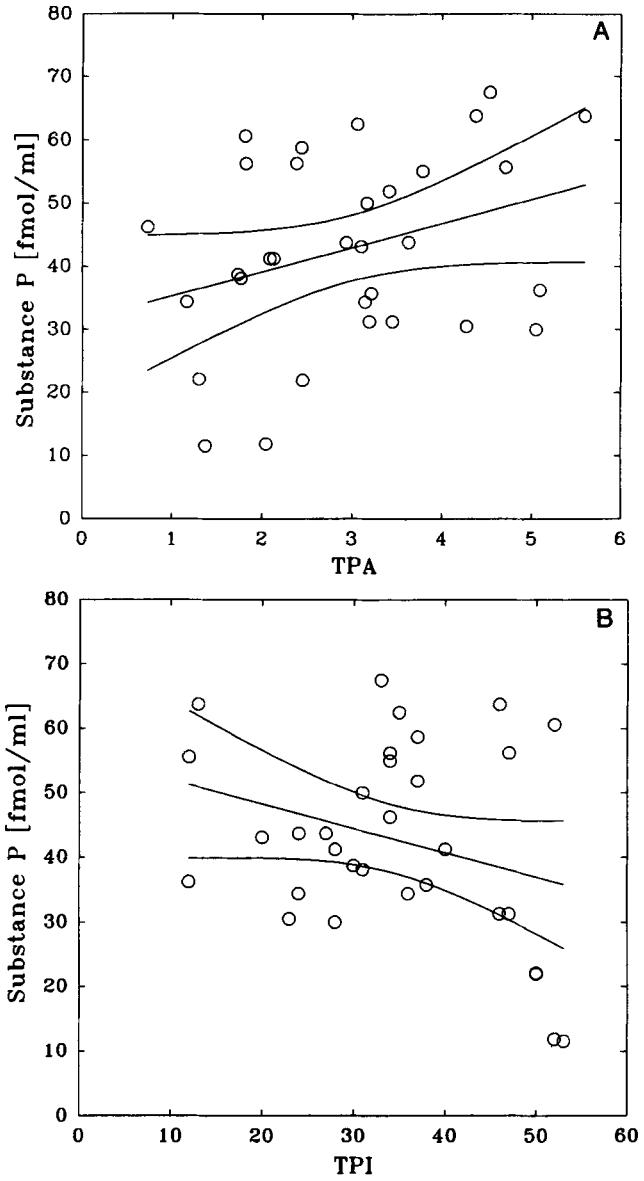

Figure 3. Substance P concentrations in cerebrospinal fluid samples from fibromyalgia patients, by average tender point threshold (TPA) (**A**) and by tender point index (TPI) (**B**). The linear plot is the least-squares line; the opposing curved lines indicate the margins of the 95% confidence bands. Note the apparent direct relationship between substance P concentration and TPA and the apparent inverse relationship between substance P concentration and TPI. Together, these curves suggest an inverse relationship between substance P concentration in the cerebrospinal fluid of fibromyalgia patients and the severity of tenderness in response to deep palpation into musculoskeletal structures.

bers release SP (42–44) to a select group of nociceptive dorsal horn neurons, which respond with slow, prolonged, excitatory, postsynaptic potentials (45). The result is a cascade of neurochemical events involving excitatory amino acids and a cyclooxygenase product (46).

Iontophoretic application of SP in the area of the lumbar dorsal horn selectively depolarizes nociceptive neurons that normally respond to chemical (47–49), thermal (50), or mechanical (51) stimuli. SP enhances evoked discharges, while an SP antagonist attenuates them (52). SP may not function as a typical neurotransmitter (53–56), but it does mediate slow, temporal summation ("windup") of C-afferent evoked

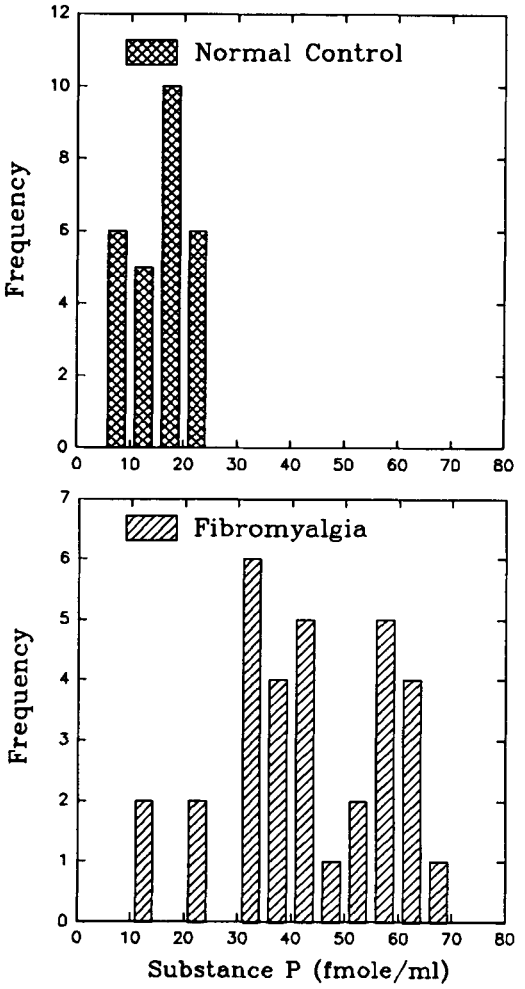

Figure 4. Numbers of normal controls and fibromyalgia patients with cerebrospinal fluid substance P concentrations within each step range (of ±5 fmoles/ml). Note that the normal controls seem to represent one cluster and that fibromyalgia patients with elevated values seem to segregate into 2 separate clusters, which lie on either side of substance P = 50 fmoles/ml.

responses in nociceptive neurons (52,57). Considering the integral relationship of SP to nociception, any defect in its production, functional activity, or degradation could result in abnormal pain perception.

The present study confirms the previously demonstrated (15) 3-fold elevation of SP in the CSF of FMS patients. The 2 study groups were prospectively investigated in parallel and their CSF samples were processed identically. The mean ages of the 2 groups were different, but age was not related to CSF SP. Therefore, it can be stated with confidence that SP is elevated in the CSF of FMS patients.

This finding, in combination with the lower-than-normal serum serotonin concentrations previously reported in other FMS patients (21–23), supports the hypothesis that biochemical interactions between serotonin and SP may be responsible for the lower-than-normal pain threshold in FMS (58). There is no clear explanation for these elevated CSF SP levels in FMS, but there are hints from animal models. Exposure of neonatal rats to an excess of SP was associated with increased spinal cord concentrations of SP in those same animals when they became adults (59). In contrast, exposure of neonatal animals to SP antisera caused a permanent decrease in the SP content of adult spinal cord and left the adult animals less responsive to SP (60).

The relevance of these observations with regard to FMS patients is uncertain. Could an environmental factor, such as a neonatal infection, induce persistently high SP levels in the central nervous system and predispose to adult FMS? By analogy, the initiator of chronic inflammatory arthritis is similarly obscure, but SP seems to act nociceptively in arthritic joints and has been found to be elevated in inflammatory synovial fluids (61,62).

One objective of this study was to analyze the clinical correlates of elevated CSF SP levels in FMS. For example, the FMS and normal control groups were different psychologically. Affective symptoms may develop in FMS patients in response to chronic pain (30). Almay et al (63) reported *lower*-than-normal CSF SP concentrations during chronic painful states and a relationship between CSF SP levels and inner tension or sadness. In contrast, the present report shows *elevated* CSF SP concentrations in FMS patients and no correlation with any psychological profile. It may be that elevation of CSF SP in FMS is unique among chronic pain states.

The pain data from the FMS patients and the controls could not be merged for the correlational analyses because the variables "pain" and "diagnosis" were so interdependent. Fortunately, there was sufficient variation of CSF SP levels within the FMS group to allow investigation for clinical correlates in that group alone. Correlations between elevated SP levels and the severity of pain in FMS (TPI, TPA) were expected, but the finding of an inverse relationship was a surprise. Those associations were weak and will require confirmation.

One hypothetical explanation for a relatively higher pain threshold (less pain) among FMS patients with very high levels of SP could follow from animal studies (64). NK1 receptors, which promote nociception after specifically binding the carboxy-terminal region of SP, may become saturated at moderate levels of SP. At even higher levels, intact SP or its amino terminal fragments could "spill over" and activate other SP receptors which inhibit nociception.

The prospect of elevated levels of SP in FMS CSF might prompt the clinician to consider CSF SP measurement as a diagnostic test, but that approach is not currently recommended. Until the specificity of this finding is better understood, or until the CSF SP level would clearly influence a therapeutic decision, prudence indicates that CSF analysis in FMS patients should remain a research endeavor.

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