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Neurophysiologic Evidence for a Central Sensitization in Patients With Fibromyalgia

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Objective. **To determine whether abnormalities of peripheral and central nociceptive sensory input processing exist outside areas of spontaneous pain in patients with fibromyalgia (FM) as compared with controls, by using quantitative sensory testing (QST) and a neurophysiologic paradigm independent from subjective reports.**

Methods. **A total of 164 outpatients with FM who were attending a self-management program were invited to participate in the study. Data for 85 patients were available and were compared with those for 40 non-FM controls matched for age and sex. QST was performed using thermal, mechanical, and electrical stimuli at locations of nonspontaneous pain. Pain assessment was 2-fold and included use of subjective scales and the spinal nociceptive flexion reflex (NFR), a specific physiologic correlate for the objective evaluation of central nociceptive pathways. Questionnaires regarding quality of life and the impact of FM were available.**

Results. **Participants were mainly middle-aged women, with a mean disease duration of 8 years. Between-group differences were significant for neurophysiologic, clinical, and quality of life measures. In patients with FM, peripheral QST showed significantly altered cold and heat pain thresholds, and tolerance to cold pain was radically reduced. The median NFR threshold in patients with FM (22.7 mA [range 17.5–31.7]) was significantly decreased compared with that in controls (33 mA [range 28.1–41]). A cutoff value of <27.6 mA for NFR provided sensitivity of 73% and specificity of 80% for detecting central allodynia in the setting of FM.**

Conclusion. **Our results strongly, although indirectly, point to a state of central hyperexcitability of the nociceptive system in patients with FM. The NFR can be used to assess central allodynia in FM. It may also help discriminate patients who may benefit from use of centrally acting analgesics.**

Despite extensive research, the etiology and pathogenesis of fibromyalgia (FM) remain unclear. This syndrome is not associated with any physical, radiologic, or biologic findings that are directly related to dysfunction, and patients generally appear to be well (1). Russell (2) relates FM to biochemical alterations in pain perceptions, and Yunus (3) has described it as a state of altered pain modulation.

The decreased pain threshold in FM is generalized, and the peripheral tissues involved are muscles, skin, bone, tendons, and ligaments. It is unlikely that so many types of peripheral tissues would be primarily involved to produce pain. Along with spontaneous widespread pain, mechanical allodynia (in which innocuous stimuli such as light touch may be perceived as painful) is a key feature of FM tender points (4). Furthermore, in most patients allodynia is not limited to tender point sites and can be caused by stimuli of lower intensities, such as muscle tension at rest (4–6).

Experimental studies in patients with FM confirmed an increased sensitivity to nonspecific stimuli such as mechanical pressure, cold, and warm sensations in areas outside tender point sites or in areas without spontaneous pain, suggesting an aberration of central pain mechanisms (4–6). Such an aberration could, at least partially, be related to altered central nervous system (CNS) processing of nociceptive stimuli and

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provides a possible explanation for generalized decreased pain tolerance and allodynia (7–9). It is now clear from experimental and human data that long-lasting noxious stimulation or damage to the nervous system can give rise to long-term changes and neuronal hyperexcitability in the spinal cord, and sensitization of the nervous system (10–12). This hyperexcitability of spinal or higher brain center neurons, also called central sensitization, plays an important role in the development and maintenance of chronic spontaneous pain and centrally mediated allodynia in various pain conditions (10,12).

In patients with FM, there is indirect evidence for a central dysfunction of the nociceptive modulating system. Metabolic or pharmacologic findings suggest involvement of the CNS in FM, such as regional modification in cerebral blood flow as well as in levels of substance P, and alteration of *N*-methyl-D-aspartate receptors or monoaminergic modulation in the spinal cord (13–19). Furthermore, abnormal neurophysiologic increase in temporal summation, expansion of receptive fields and hyperalgesia after electrical stimulation, alteration of the nociceptive modulating system, and late evoked potentials have been reported in patients with FM (4,7,20–23). These findings, which have also been reported in other chronic pain syndromes, suggest a neurogenic component of sensory abnormalities in patients with FM that might be explained in terms of central sensitization of nociceptive afferent pathways (3,24).

This study aimed to determine whether abnormalities of peripheral and central nociceptive sensory input processing exist outside areas of spontaneous pain in patients with FM as compared with non-FM controls, by using quantitative sensory testing (QST) and a neurophysiologic paradigm independent from subjective reports.

PATIENTS AND METHODS

Patients. Participation in the study was proposed to 164 consecutive outpatients with FM who were included in a randomized controlled trial of a self-management–based program (25). The patients enrolled in this program were referred by their general practitioners, internists or rheumatologists to the divisions of Rheumatology and Reeducation at the Geneva University Hospital. The inclusion criterion for the neurophysiologic assessment was fulfilling the American College of Rheumatology 1990 criteria for FM (26). Noninclusion criteria were specific medical disorders (e.g., fractures, infectious or neurologic diseases) and inability to interrupt therapy with analgesics (nonsteroidal antiinflammatory drugs, opioids) or coanalgesics (antidepressants, anticonvulsants) for at least 15 days; use of rescue analgesics with a short half-life (e.g., acetaminophen) for up to 24 hours before the examination was allowed.

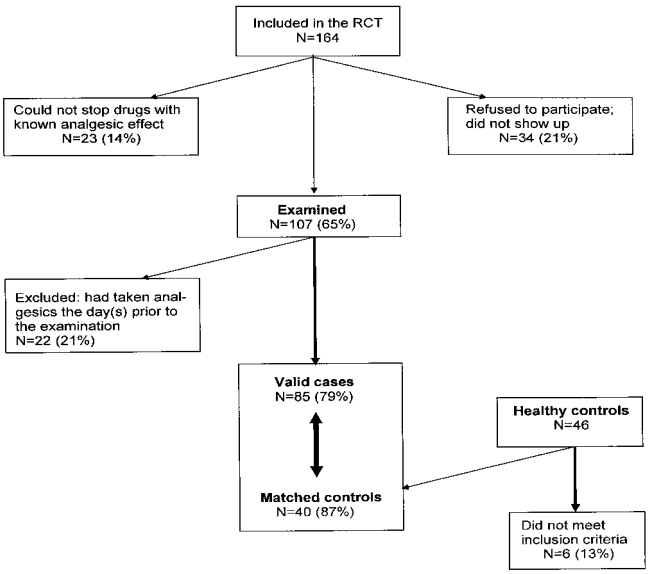

Figure 1. Flow diagram of inclusion in the study. RCT = randomized controlled trial.

Of the initial sample of 164 patients examined by the rheumatologists or physiatrists, 23 were not able to interrupt use of analgesics, and 34 refused to participate. A total of 107 patients underwent a neurophysiologic examination. Twenty-two of the 107 subjects (21%) were further excluded because of intake of central analgesics in a time frame that could interfere with the examination. The final analysis was performed based on the neurophysiologic examinations of 85 (79%) of the 107 patients. Figure 1 shows the flow diagram of inclusion in the study (27).

The control group was recruited by asking the patients to bring someone from among their close circle of friends who was matched for age and sex, had no acute or chronic health problems, and was taking no medication. A rheumatologist performed a medical evaluation to assess the absence of chronic medical disorders affecting the peripheral or central nervous system, a chronic painful condition, or use of medication. Of the 46 control subjects who were recruited, 6 (13%) were excluded (e.g., for chronic low back pain), and 40 (87%) underwent the neurophysiologic examination. The protocol was approved by the local ethics committee, and prior written informed consent was obtained from all participants.

Clinical measures. The 18 tender points and the myalgia score were assessed in patients and controls by the rheumatologist or physiatrist. In response to a digital force of 4 kg, subjects were asked to indicate whether they felt no discomfort (score = 0), tenderness (score = 1), or pain; pain with no grimace, flinching, or withdrawal was scored as 2, and pain with grimace, flinching, or withdrawal was scored as 3. The myalgia score can range from 0 to 54. The evaluating physician's global impression (PGI) of the patient's general

status was scored on a 5-point scale (1 = best). As part of the evaluation of the self-management–based program, patients with FM completed the Regional Pain Score (RPS) instrument (28) and validated quality of life questionnaires, i.e., the Psychological General Well-Being (PGWB) index (29), 4 subscales of the Short Form 36 (SF-36) (30), and the Fibromyalgia Impact Questionnaire (FIQ) (31). Assessment of the control group included use of the same questionnaires, except the FIQ.

The RPS is a drawing of the human body on which 21 regions are indicated. Participants were asked to assess pain in each region by indicating the level that best described it, from 0 (no pain) to 5 (unbearable pain), providing a total score between 0 (best) and 105 (worst). The RPS has been validated in patients with FM.

The PGWB index was designed to assess subjective feelings of psychological well-being and distress and has been used previously in patients with FM (32–34). It measures self-reported positive and negative affective states and characterizes the psychological dimension of health-related quality of life. The PGWB index includes 6 subscales, for a total of 22 items measuring anxiety, depression, general health, positive well-being, self-control, and vitality. Each item is scored from 0 to 5, providing a total score between 0 and 100, with higher values indicating more positive responses. The SF-36 is a nonspecific health and functional status questionnaire (30). The subscales for general health, physical functioning, role-physical and social functioning were applied. Scores for each subscale range from 0 (worst) to 100 (best). The subscales for role-emotional, mental health, and vitality were not included because of overlap with the PGWB index.

The FIQ is a condition-specific, widely used, reliable, and valid questionnaire, with higher scores indicating negative impact. It consists of 10 subscales assessing physical function, number of days feeling bad, work missed, job ability, pain, fatigue, morning tiredness, stiffness, anxiety, and depression (31).

QST, neurophysiologic measures. The testing session always took place in the morning and in the same quiet, temperate (24°C) room. Subjects were exposed to ambient temperature for 10–15 minutes. They were not permitted access to the QST computer screen and were not given visual or auditory cues to indicate the start of a stimulus. Spontaneous pain was assessed, using a 10-cm visual analog scale (VAS). Experimental pain was then investigated both subjectively and objectively by means of validated techniques. These techniques are used to explore the peripheral and central nociceptive pathways by applying various stimuli at locations of nonspontaneous pain.

Peripheral nociceptive pathway tested by thermal stimulation. *Thermal perception, cold and hot pain thresholds.* Thermal stimulations were graded in order to evaluate peripheral thermal perception first, then thermal pain thresholds and thermal pain tolerance to a maximal painful stimulation. Thermal thresholds were measured by means of a thermal sensory analyzer (Medoc Advanced Medical Systems, Ramat-Yishai, Israel). The thermal sensory analyzer operates by a microcomputer-driven 3-cm × 3-cm (9 cm^2) Peltier contact thermode. The entire thermode-stimulating surface was placed in contact with the glabrous skin in the inside of the forearm testing site and secured by a Velcro band. The stimulation surface was heated and cooled within a range of 0°C to 50°C. The gradients of the change of each stimulation were linear and were set to 1°C/second, with a baseline temperature of 32°C. The cold threshold was systematically used as a first evaluation. The perception and pain thresholds were assessed using the method of limits (mean of 4 measures) (35–38).

Cold pressor test (or pain tolerance). The cold pressor test was used to assess pain tolerance to a tonic, intense pain stimulation (39–41). This test stimulates peripheral C fibers and consists of hand immersion in an iced water bath. The device consists of a container divided by a mesh screen: one side is filled with ice that maintains the water on the other side at ~0°C. A stirring device circulates the water, and the temperature of the water near the hand is monitored by a thermosistor with a digital display (± 0.1°C). The mesh screen prevents direct contact between the ice and the skin of the subject.

Subjects were instructed to keep their hand in the water until the sensation experience was "the maximum bearable" (the cutoff time was 2 minutes, in order to avoid any tissue lesions). The results for pain tolerance were expressed as the latency period of withdrawal, and pain intensity at this time was evaluated by a VAS.

Central nociceptive pathways tested by electrical stimulation. *The nociceptive flexion R-III reflex (NFR).* The NFR is considered to be a specific and objective physiologic correlate of pain sensation (42–50). More recently, this method has gained particular attention as a research tool in studies of central sensitization, because this reflex is obtained after electrical stimulation applied directly to the sural nerve, circumventing peripheral nociceptors and directly stimulating the nociceptive pain pathway. Psychophysiologic studies confirmed that the NFR is a reliable tool for assessing the central antinociceptive effects of analgesics or other therapeutic approaches (51–57).

Briefly, subjects rested comfortably in a supine position in order to obtain muscular relaxation. Cutaneous electrodes were applied, and the sural nerve was stimulated in its retromaleolar track. The electrical stimulus consisted of single rectangular impulses (0.5 msec) delivered with 6–10 second interstimulus interval, by a constant current stimulator at variable intensities (1–100 mA) (Nicolet Viking IV; Nicolet, Madison, WI). Electromyographic responses were recorded using a pair of surface electrodes placed over the tendon of the ipsilateral biceps femoris. The R-III reflex (objective threshold) was identified as a multiphasic signal appearing at least 90 msec but less than 250 msec after each stimulation and was considered to be present when the corrected computed surface was >0.5 mV/msec (positive response). Subjects were instructed that the sensation intensity could randomly increase, decrease, or stay the same, with stimulus repetition occurring independently of their answers.

Following electrical stimulation of the sural nerve, patients were asked to describe what they felt using 3 scales: 1) numerical rating scale from 0 (no pain at all) to 10 (worst pain imaginable), with 4.5 as a cutoff for painful sensation (positive response); 2) sensitive scale with 7 categories (from nothing to very strong pricking or burning sensation); and 3) affective scale with 7 categories (from nothing to unbearable). Subjective and objective pain thresholds were then defined as the intensity of current inducing 50% of positive responses to a

Table 1. Sociodemographic characteristics and clinical pain severity in patients with fibromyalgia and controls*

Characteristic	Patients (n = 85)	Controls (n = 40)	*P*
Age, years	49 ± 9.3	47 ± 12.2	NS
Sex, % women	89	87.5	NS
Education			
% completed elementary school	45	28	–
% completed high school	46	65	NS
% completed university	7	7	–
Employment status			
% employed	17	80	<0.01
% not working/retired	14	19	–
% on sick leave	23	0	–
% on disability	46	1	–
Clinical pain severity			
Mean duration of symptoms, years (range)	8 (0.5–49)	–	–
No. of tender points (0–18 scale)	16 ± 2.8	0.6 ± 2.1	<0.0001
Myalgia score (0–54 scale)	28 ± 8.9	0.6 ± 2	<0.001
Regional pain score (0–105 scale)	65 ± 16.9	12.4 ± 11.2	<0.001
Pain at time of neurophysiologic examination (10-cm VAS)	5.6 ± 0.3	0.56 ± 1.7	<0.001
Antidepressant analgesics			
% using none	37	100	–
% using tricyclic	32	–	–
% using serotonin reuptake inhibitor	21	–	–
% using noradrenergic	2	–	–
% using other	8	–	–

* Except where indicated otherwise, values are the mean ± SD. VAS = visual analog scale.

series of 30–40 stimulations and were obtained by fitting the percentage of positive responses to Hill's equation.

Diffuse noxious inhibitory control (DNIC). In man, experimental painful counterirritative conditioning stimuli applied at a heterotopic level (e.g., the elbow) induces parallel decreases in the amplitude of the NFR, and the inhibition parallels the intensity of the conditioning stimulus, whereas non-nociceptive stimuli are usually without effect. Such phenomena are related to DNIC and are sustained by a loop involving nociceptive supraspinal structures (58–62). Tonic stimulation of the ipsilateral elbow tender point site in both FM and control groups was tailored to deliver an expected, normally nonpainful mechanical stimulation by always keeping the dolorimetric pressure under 4 kg/cm^2. When a normally nonpainful mechanical stimulation induced a pain sensation, we avoided producing more than moderate pain on a VAS (no more than 5 of 10). Under normal conditions, this theoretically "non-nociceptive" mechanical stimulation should not modify the amplitude of the NFR, because the nociceptive pathway should not be activated (63).

Statistical analysis. The demographic characteristics of the patients and controls were compared by chi-square tests for categoric data, and by a *t*-test for continuous data. Subjective and objective neurophysiologic measures of FM were compared using the Mann-Whitney U test, because most of the data were not normally distributed. All parametric values are expressed as the mean ± SD, and the nonparametric values are expressed as the median and ranges. *P* values less than 0.05 were considered significant. The analyses were performed using SPSS version 9.0 software (Chicago: SPSS; 1999). Spearman's rank correlation coefficients were calculated for the objective and subjective experimental measurements and clinical variables. A receiver operating characteristic (ROC) curve was constructed as a continuous function of sensitivity (true-positive rate) versus 1-specificity (false-positive rate), by considering various possible values of the NFR threshold.

RESULTS

Clinical characterization of the population. Comparison of the sociodemographic and clinical variables between patients and controls showed statistically significant differences for all variables except the matching variables of sex, age, and education (Table 1). The majority of subjects were female; the mean (±SD) age was 49 ± 9.3 years and 47 ± 12.2 years in patients and controls, respectively, and most of the subjects had completed at least compulsory school.

The mean duration of FM symptoms was 8.0 years (range 0.5–49 years). At the time of the neurophysiologic examination, patients rated their pain as a mean ± SD of 5.6 ± 0.3 on a 10-cm VAS. All measures of clinical severity indicated severe pain, and 63% of FM patients versus 0% of the control group had been taking

Table 2. Results of the PGWB and the SF-36 in FM patients and controls*

	Patients	Controls	*P*
PGWB			
Anxiety	11.4 ± 5.3	18.5 ± 3.3	<0.001
Depression	8.3 ± 3.9	13.1 ± 1.4	<0.001
General health	5.2 ± 2.2	12.1 ± 2.3	<0.001
Positive well-being	8.1 ± 3.9	13.7 ± 2.5	<0.001
Self-control	6.8 ± 3.3	12.2 ± 1.4	<0.001
Vitality	6.6 ± 3.6	14.3 ± 0.4	<0.001
Total score (range 0–110)	46.3 ± 14.1	83.9 ± 11.6	<0.001
SF-36			
Physical functioning	44.9 ± 19.8	91.3 ± 20.7	<0.001
Role-physical	14.2 ± 28	92 ± 17.9	<0.001
General health	33 ± 19	80 ± 15.3	<0.001
Social functioning	34 ± 20.7	88.1 ± 13.6	<0.001

* Values are the mean ± SD. PGWB = Psychological General Well-Being; SF-36 = Short Form 36; FM = fibromyalgia.

Table 3. Thermal perceptions, pain thresholds, and cold pressor test in patients with FM and controls*

	Patients	Controls	*P*
Cold perception, °C	30.35 ± 0.88	30.18 ± 1.14	0.37
Warmth perception, °C	34.59 ± 1.16	34.31 ± 0.78	0.23
Cold pain threshold, °C	17.58 ± 9.05	10.49 ± 9.3	<0.001
Hot pain threshold, °C	41.20 ± 4.36	43.90 ± 6.14	0.005
Cold pressor pain tolerance, seconds	16.1 ± 15.61	47.67 ± 38.50	<0.001

* Values are the mean ± SD. FM = fibromyalgia.

antidepressants. The measures of quality of life also showed important impairments in patients with FM (Table 2). Ratings were at the high end of the rankings for depression, anxiety, and impaired quality of life.

Quantitative sensory testing. *Results of peripheral nociceptive pathway testing (Table 3).* Thresholds for cold or warm sensation were similar for both groups. Compared with controls, patients had significantly lower cold and heat pain thresholds ($P < 0.001$ and $P = 0.005$, respectively). Tolerance to cold pain was severely reduced (by 66%) in patients with FM ($P < 0.001$). Pain intensity (as measured on a 10-cm VAS) at the time of hand withdrawal was significantly higher in patients (8.2 ± 1.6 versus 7.3 ± 1.7 in controls; $P < 0.05$). In patients with FM, the mean latency period before hand withdrawal was 13 seconds, compared with 28 seconds in control subjects, 6 of whom reached cutoff values (120 seconds) ($P < 0.001$).

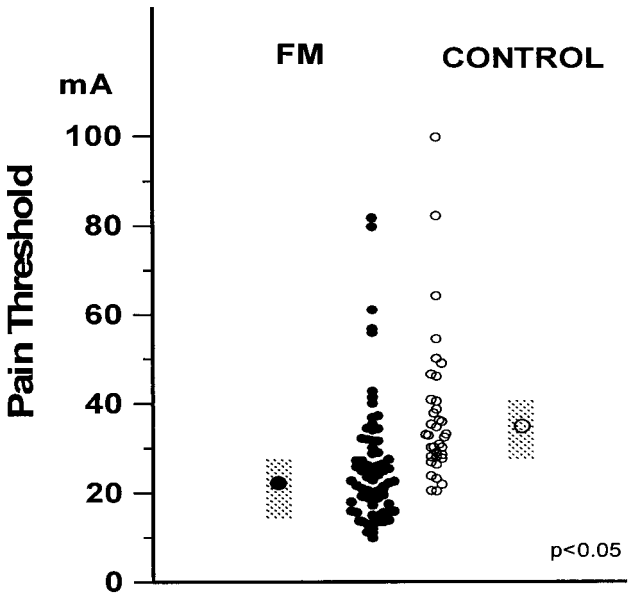

Figure 2. Nociceptive flexion reflex threshold in patients with fibromyalgia (FM) and controls. Cross-hatched areas represent the interquartile interval; circles within the cross-hatched areas represent the median.

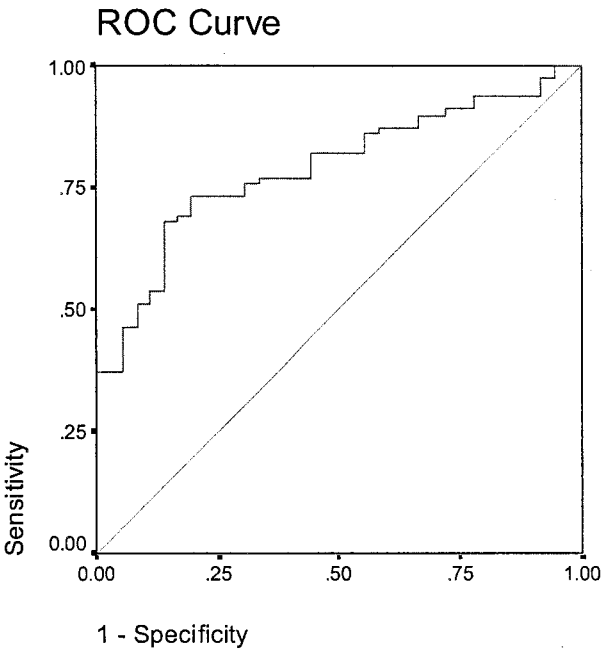

Figure 3. Receiver operating characteristic (ROC) curves for nociceptive flexion reflex measurements.

Results of central nociceptive pathways testing. The NFR threshold was decreased by 33% in FM patients ($P < 0.001$) (Figure 2). The median values of NFR threshold (22.7 mA [interquartile range 17.5–31.7]) was significantly decreased (by one-third) as compared with control (33 mA [28.1–41]). The following optimal discriminatory threshold values were chosen, and a cutoff value of <27.6 mA for the NFR led to sensitivity of 73.1% and specificity of 80.4% for FM patients; the area under the ROC curves (AUC) was 0.789 (95% confidence interval 0.707–0.872; $P < 0.001$) (Figure 3).

Subjective variables assessing experimental pain (numeric and categoric scales) after electrical stimulation were equally decreased in FM patients and controls. DNIC was observed in a larger proportion of FM patients than control subjects (Figure 4). The amplitude of the NFR (as described by the AUC) was decreased (>20%) despite conditioning stimulation of <4 kg/cm^2 of the ipsilateral elbow in >50% of FM patients compared with <30% of control subjects.

Correlation between experimental and clinical variables. Under standardized conditions, using increasing stimulus strength, a close relationship was observed between the NFR amplitude and the pain score as a

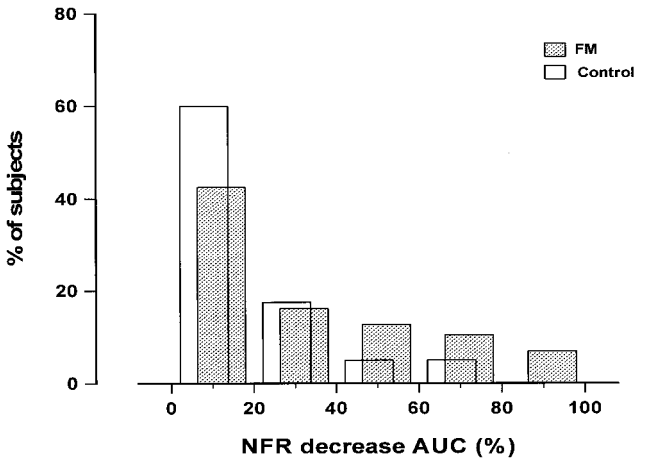

Figure 4. Percentage of decrease of nociceptive flexion reflex (NFR) amplitude during allodynic stimulation (<4 kg/cm^2) of ipsilateral elbow tender points in patients with fibromyalgia (FM) and controls. AUC = area under the curve.

function of stimulus intensity (r = 0.67). Thus, an increase in the reflex size was associated with an increase in pain intensity ratings. Subjective variables assessing experimental pain (numeric scales) after electrical stimulation were closely and positively correlated with perceptive and affective pain thresholds (categorical scales) in FM patients (r = 0.67 and r = 0.74, respectively, $P <$ 0.01), to hot and cold pain thresholds, and to the cold pressor test (r = 0.38, r = 0.34, r = 0.42, respectively, $P < 0.01$). Similar correlations were observed in the control subjects. None of the clinical variables assessing the duration or severity of illness was correlated with the experimental subjective or objective pain assessments, except the NFR threshold, which was inversely correlated with the PGI score (r = -0.27, $P < 0.05$).

DISCUSSION

A decrease in the NFR and the subjective pain thresholds to electrical stimulations is a key result of our study and brings forth psychophysical evidence of abnormally processed input to central nociceptive pathways in patients with FM. Furthermore, detection thresholds for perception evoked by thermal stimulation were similar in FM patients and controls and corresponded to the expected quantitative sensory testing values in this population (7). These results confirm the absence of peripheral large and small nerve fiber lesions. FM may be the consequence of modified stimulus processing by the CNS without recognizable peripheral sources of nociceptive input or peripheral nerve dysfunction (64). These results can be discussed in both pathophysiologic and diagnostic terms.

In contrast to methods that are commonly used to trigger painful sensations by stimulating input from peripheral nociceptors with thermal stimulation or mechanical pressure, electrical sural nerve stimulation techniques bypass transduction mechanisms of peripheral nociceptors and nonselectively activate A delta and unmyelinated C fibers (65,66). Subjective pain thresholds after electrical stimulation of the sural nerve, which is usually an area of nonspontaneous pain in FM patients, were consistently decreased in patients compared with controls. The NFR threshold obtained after sural nerve stimulation was also radically and consistently decreased in FM patients compared with control subjects. These electrophysiologic observations may be explained in terms of central sensitization of afferent nociceptive pathways and are consistent with other recent observations of abnormally low pain thresholds and allodynia in FM patients outside areas of spontaneous pain and in other chronic pain conditions (4–6,13,18,67).

Using normally nonpainful mechanical stimulation of the elbow, DNIC was elicited in a substantial proportion of patients with FM, in sharp contrast to control subjects (Figure 4). It has been established that DNIC can be activated only when subjects undergo intense nociceptive stimulation driven by unmyelinated afferents, whereas non-nociceptive stimuli are without effect (68,69).

In FM patients, a trigger stimulation of <4 kg/cm^2 led to activation of DNIC, suggesting that allodynia in patients with FM is preferentially mediated by nociceptive pathways (70,71). The effectiveness of mechanical stimuli in triggering DNIC reinforces the hypothesis of central sensitization and a possible alteration of the central modulatory inhibitory pathways in patients with FM (22,23).

Allodynia has been described as an important feature of central sensitization that can be ascribed to increased excitability and enlarged receptive fields of dorsal horn and supraspinal neurons (4). In our study, experimental evaluations were not correlated with the clinical severity and duration of FM symptoms. This could be partly explained by the fact that experimental stimulations were applied outside a region of spontaneous pain. Accordingly, and in addition to clinical diagnostic evaluation, this indirect electrophysiologic evidence of central sensitization (e.g., decreased NFR) could be further used as a diagnostic assessment of allodynia in patients with FM. Despite large interindi-

vidual variability of the objective pain threshold (Figure 2), the cutoff value of <27.6 mA for the nociceptive pain threshold led to fair sensitivity (73%) and good specificity (80%) for detecting central allodynia in these patients. These findings suggest that the NFR threshold measurement might be used to discriminate FM patients who may benefit from centrally acting analgesics such as antidepressants. Indeed, antidepressants have already been shown to modify and increase the NFR threshold after a single dose in healthy volunteers (72).

Some limitations of the study should be mentioned. There may be a recruitment bias in the control groups, because it was constituted by asking patients to bring someone from their close circle of friends. However, the values of the 4 subscales of the SF-36 (physical functioning, role-physical, general health, and social functioning) that have been used were within the range of those for healthy individuals (73). The same was true for the PGWB index (29). As for the neurophysiologic examination, quantitative sensory testing values were within the range of those expected in a normal population.

The majority of published clinical studies of the NFR were conducted in healthy volunteers. Only a few controlled studies involving patients with sciatica, painful diabetic neuropathy, pain after lumbar disc surgery, and patients with different types of chronic headache have been published (74–77). The specificity of a decreased NFR threshold has not been systematically tested in other chronic pain syndromes involving mainly women and thus cannot be considered a diagnostic tool in FM. In a study of another episodic chronic pain condition (cluster headache) involving 56 patients, 2 of whom were female, an episodic decrease in the NFR threshold was reported, leading to the conclusion that CNS nociceptive intermittent dysfunction was likely (67). Another study assessed the NFR in 53 patients (39 of whom were female) with various chronic pain syndromes other than FM (78). No differences were found between controls and patients, and no correlation between experimental pain measures and clinical pain was observed. These later observations led to the assumption of the absence of central dysfunction in patients with chronic pain. However, conclusions could have been hampered by the relatively small number of patients and, moreover (and most importantly), by the concomitant intake of centrally acting analgesics. Thus, the specificity of the NFR decrease in patients with FM compared with that in patients with other chronic pain syndromes needs further investigation.

In our study, patients had a 2-week washout period before the neurophysiologic examination. We also checked the possibility that decreased pain thresholds in FM may be attributable to withdrawal of psychotropic drugs (i.e., we compared the NFR in FM patients preexposed to psychotropic drugs with that in FM patients with no prior exposures). No substantial differences, excluding a withdrawal syndrome, were observed that could account for our results. However, the important issues of spontaneous diffuse pain, washout of psychotropic drugs, and flare in FM patients still need to be systematically addressed in a prospective, longitudinal study.

The perceived heightened intensity of electrical stimulation and the decrease in nociceptive pain thresholds for such a large variety of stimuli (e.g., hot, cold, mechanical, electrical) may be an expression of a generalized hypervigilance and may mirror an adaptation to the chronic pain experience. In our study, this generalized hypervigilance may account for the correlation between the NFR threshold and the PGI. This impression may translate the feeling that the whole somatosensory system is activated. Studies comparing evoked potentials after painful versus auditory stimulation in patients with FM suggest that the increase in perceived intensity may selectively affect nociceptive pathways (79). Other studies point to specific rather than generalized hypervigilance (80). In our study, the pain threshold to hot and cold stimulation was significantly lower in patients with FM and was consistent with the diffuse hyperexcitability and sensitization phenomenon affecting the nociceptive system. Two studies suggest that aberrant thermal perceptions could be attributable to a dysfunction at the level of the limbic cortex, and that cooling supraliminary stimulations could be abnormally integrated in the insula and generic of FM patients (7,81).

Other critical questions such as the extent to which central sensitization precedes or is the consequence of repeated nervous system "injuries," and whether the expression of central sensitization is a predominantly gender-related phenomenon, remain to be answered.

In conclusion, when pooled with the current literature, our results strongly, although indirectly, point to CNS sensitization in patients with FM. Our observations suggest a state of central hyperexcitability of the nociceptive system. The nociceptive flexion reflex could be applied as a complementary indicative tool of a state of central allodynia in patients with FM, and additional prospective studies are required to ascertain whether the NFR would help to identify patients with FM who may

benefit from the use of centrally acting analgesics such as antidepressants.

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