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# Possible Deficiencies of Pain Modulation in Fibromyalgia

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## Abstract: TOP

Objective: To examine possible deficiencies in endogenous pain modulating mechanisms in fibromyalgia patients compared with matched pain-free control subjects.

Design/Subjects/Methodology: Pain reduction was investigated in 25 female patients with fibromyalgia and 26 age-matched healthy women using the diffuse noxious inhibitory controls (DNIC) paradigm. Tonic thermal stimuli at painful and nonpainful intensities, tailored to individual heat pain thresholds, were employed to induce pain inhibition. The anticipated effect was assessed by measuring the electrical pain threshold and detection threshold, using a double staircase method. Only nontender control points were stimulated (thermode on the foot, electrodes on the inner forearm).

Results: The patients with fibromyalgia had significantly lower heat pain thresholds than the healthy subjects, but similar electrical detection and pain thresholds. The repeatedly applied electrical stimuli resulted in a degree of perceptual adaptation that was similar between the two groups. However, concurrent tonic thermal stimuli, at both painful and nonpainful levels, significantly increased the electrical pain threshold in the healthy subjects but not in the fibromyalgia patients. The electrical detection threshold was not affected in either group.

Conclusions: Pain modulation, produced by a concurrent tonic stimulus in healthy persons, was not seen in the fibromyalgia group. The patients either had deficient pain modulation or were unable to tolerate a tonic stimulus intense enough to engage a modulatory process. It remains to be established whether the pain reduction found in the healthy subjects was the conventional DNIC effect, another effect (e.g., distraction), or a combination of both.



The chronic pain syndrome, fibromyalgia, is characterized by diffuse, widespread pain and the presence of multiple tender points at characteristic sites.[1] Numerous studies have demonstrated pain hyperresponsiveness among fibromyalgia patients, not only at the designated tender points but also at various other body locations.[2-7] Recently, we found a similar pattern of generalized hyperresponsiveness when heat

pain instead of pressure pain was applied[8] and when patients were presented with bursts of white noise.[9]

To account for the widespread endogenous pain and the hyperresponsiveness to induced discomfort, several theoretical proposals have been advanced. Psychological approaches center around the idea that persons who are inclined to amplify unpleasant experiences are hypervigilant to painful events and, as a consequence, are at risk of developing fibromyalgia.[9-11] Some biological perspectives acknowledge a peripheral contribution by assuming a sensitization of muscle nociceptors. However, it has become increasingly obvious that central pathophysiologic mechanisms must be invoked to account for other elements of fibromyalgia.[11-14]

Dysfunctions of central pain inhibitory mechanisms could explain the wide anatomic spread of pain when fibromyalgia develops following a localized pain problem, as it often does. It is as if an inhibitory barrier limits the spread of pain in normal persons but fails in fibromyalgia patients.[15] Some authors[14,16] have imputed low levels of central serotonin for insufficient pain inhibition.

Functional tests of central pain inhibitory mechanisms in humans have become available through procedures that investigate "diffuse noxious inhibitory controls" (DNIC).[17-19] DNIC is an explanatory hypothesis for the finding that a strong sustained pain decreases pain responsiveness in a heterotopic fashion (i.e., a pain at one locus is capable of reducing pain at multiple other loci). This mechanism appears to be the sort of barrier that is capable of preventing a spread of pain to other body parts. Hence, it is tempting to assume that a deficiency in a DNIC-like mechanism may underlie the widespread pain in fibromyalgia.

Others have also suggested that a deficiency in pain inhibition might be responsible for the development of chronic pain. For example, Willer and colleagues[20,21] and Peters and colleagues[22] investigated whether acute or chronic back pain is capable of activating DNIC, obtaining mixed results. To our knowledge, few attempts have yet been made to study DNIC-like mechanisms in chronic pain patients using the usual methodology, whereby an experimental tonic pain stimulus is used as the conditioning stimulus and an experimental phasic pain stimulus as the test stimulus.[23-25] This approach offers the clear advantage of using experimentally induced pain to test potentially pathologic pain inhibition.

Consequently, the major aim of the present study was to investigate pain modulation in fibromyalgia patients and healthy persons, testing whether the alteration of phasic pain by a noxious tonic stimulus, which is the essence of the established DNIC paradigm, might be weakened or absent in the fibromyalgia group. The conditioning stimulus was a noxious tonic heat stimulus, produced according to the recently developed Tonic Heat Pain Model.[26] This procedure evokes sustained pain by applying pulsating contact heat slightly above the pain threshold. It also allows one to generate tonic heat of nonpainful quality as a control condition. The test stimulus was a phasic electrical stimulus.

The effects of tonic heat pain and tonic non-noxious heat on both electrical detection and pain thresholds by means of a double staircase procedure were assessed.[27] The staircase method also allowed us to study perceptual adaptation due to repeated electrical stimulation, a process that might be expected to differ between chronic pain patients and health persons.[22,28] To avoid excessive discomfort in persons who were already suffering from clinical pain at the time of the investigation, the procedures, which made use of two experimental pain stimuli, were designed in a manner that tailored the intensity of the noxious stimuli to individual pain responsiveness.

# METHODS TOP

## Subjects TOP

Twenty-six female patients diagnosed as having fibromyalgia according to the criteria of the American College of Rheumatology[1] took part in the study **(Table 1)**. They were outpatients of the Rheumatic Disease Unit, University Hospital, London, Ontario, Canada. Because of the severity of their disorder, those who were taking medication were allowed to continue their usual dosage. Subjects with concomitant rheumatoid arthritis were excluded, but not those with other medical problems. One patient did not complete the study and was omitted from statistical evaluation. Hence, 25 patients were considered. The patients suffered from severe fibromyalgia pain at the time of investigation, according to scores on the Localized Pain Rating[29] for present pain (see **Table 1**) and had experienced fibromyalgia pain for 121.4 ± 94.3 months. These patients also took part in a second study, for which the patients' pain characteristics were described in detail by Lautenbacher

and associates.[8] An agecomparable group of pain-free women (n = 26) was recruited by advertisement and personal contact (see Table 1).

TABLE 1. Means (±SD) of age, height, weight, and scores on the Localized Pain Rating for present clinical pain

All subjects were paid for participation. The study protocol was approved by the University's Health Sciences Ethics Committee.

## Apparatus and Procedure TOP

The subjects completed some pain questionnaires and a series of tests on pain perception and thermal sensitivity (results in reference 8). Following this, the subjects participated in the current investigation that used entirely different paradigms and stimulus conditions. There were four experimental blocks. In each block, the sensitivity for nonpainful (detection threshold) and painful (pain threshold) electrocutaneous stimuli were tested. Blocks 1 and 4 had no additional stimulation ("No Heat"). In Block 2 and Block 3, either tonic painful heat or tonic non-noxious heat were applied, resulting in two conditions, "Painful Heat" and "Nonpainful Heat." The sequence of these two conditions was reversed for half of the subjects, in a random manner, to control for order effects.

The electrical stimuli were delivered by a constant-current stimulator (CCS-1, Frederic Haer and Company, Bowdoinham, ME, U.S.A.) and consisted of 15 4-ms monophasic square-wave pulses with a stimulus onset asynchrony of 10 ms (100 Hz). These parameters resulted in a duration of 144 ms per stimulus train. The skin was cleaned and abraded; afterward, two monopolar electrodes (13L20; Dantec Medical, Skovlunde, Denmark) with a surface area of 0.3 $cm^2$ were attached 5 cm from each other, slightly to the left and right of a point in the center of the inner forearm. The start of each stimulus was signaled by a light.

A total of 80 stimulus trains, arranged in 4 blocks of 20 stimuli, were administered. In each block, 10 stimuli were included for assessment of detection threshold and 10 stimuli for assessment of pain threshold, using a modified multiple staircase method.[27] Stimuli were presented pairwise, so that if trial 1 was close to the detection threshold level, trial 2 was close to pain threshold, and so on, with the order of each pair (detection or pain) randomized.

The starting value of each staircase was the detection or pain threshold obtained in the first portion of each session.[8] Subjects were given five practice trials per staircase in order to familiarize them with the procedure and to stabilize performance. Then, the staircase was used to obtain ongoing estimates of electrical detection and pain threshold.

The stimulus intensities in the detection threshold and pain threshold staircases were varied, depending on the subject's ratings on a 6-point scale. The response classes were: 1 = No Sensation, 2 = Slight Sensation, 3 = Moderate Sensation, 4 = Strong Sensation, 5 = Slight Pain, and 6 = Moderate Pain. The decision rules for the detection threshold staircase were: after a rating of 1, go up 0.15 mA; after 2, go down 0.075 mA; and after 3 or greater, go down 0.15 mA. For the pain threshold staircase they were: after a rating of 3 or less, go up 0.3 mA; after 4, go up 0.15 mA; after 5, go down 0.15 mA; and after 6, go down 0.3 mA. Thus, subjects' electrocutaneous detection and pain thresholds were tracked over each of the four blocks, including the two in which the phasic electrical pulses were accompanied by concurrent tonic thermal stimuli at either warm or painfully hot levels.

The tonic thermal stimuli were delivered to the foot by means of a Peltier thermode (stimulation area: 6 $cm^2$; contact pressure: 0.4 $N/cm^2$) at the lateral dorsum pedis. The temperature-controlled contact thermode was mounted on an articulated arm and was part of the PATH Tester MPI 100 (PHYWE, Göttingen, Germany) (for technical details, see reference 30). The tonic stimuli were delivered according to the Tonic Heat Pain Model.[26] In this procedure, the heat pain threshold on the foot was determined twice at the beginning of Blocks 2 and 3, using a threshold adjustment procedure. The first threshold was taken as a practice run, and

the second threshold value served as the reference temperature for the subsequent painful or nonpainful tonic stimulation.

In the "Painful Heat" condition, saw-tooth-shaped heat pulses were administered at a constant frequency of 30 pulses per minute. The pulses were tailored to have a base of 0.3°C below the reference temperature and a peak temperature of 1°C above it (so that, for example, an estimate of 44°C led to pulses with a base of 43.7°C rising to a peak of 45°C). In the "Nonpainful Heat" condition, the procedure was the same with the exception that the peak was 0.3°C below and the base 1.6°C below the pain threshold reference temperature obtained at the start of that block. This approach allowed the effects of tolerable tonic heat pain, which slowly increased in intensity and unpleasantness, to be compared with the conditioning effects of a strong but nonpainful tonic heat stimulus.[26]

Thermal stimulation was maintained in both Blocks 2 and 3 until all 20 electrical stimuli had been delivered, resulting in a tonic stimulation period of about 5 minutes in each. The interval between the blocks was 1 minute.

## Evaluation TOP

As adaptation may occur when electrical stimuli are repeatedly applied (as found, for example, by Ernst and colleagues[31] in a study that used tooth pulp stimulation and Higashiyama and Tashiro[32] for skin stimulation), we computed linear regressions for both staircases separately in each subject. The intercept was used as the measure of initial sensitivity and the slope, over the course of the experiment, as the measure of adaptation. To examine changes in detection and pain threshold that went beyond the effects of simple adaptation (i.e., that were caused by the suppressive effects of tonic thermal stimulation on electrical phasic pain), the residuals (average = 0) were computed. The computation was carried out across the 40 stimuli of each staircase, so that an increase in either threshold during tonic heat stimulation would raise the data points away from the regression line, creating positive residuals, and consequently, the residuals during the "No Heat" conditions would have negative values.

An example of the data obtained from a single fibromyalgia patient is shown in **Figure 1**. The data points for both detection and pain threshold staircases during conditions of no concurrent heat, nonpainful heat, and painful heat are fit by regression lines and allow a determination of both initial sensitivity and adaptation. The differences between the staircase values and the regression lines during the concurrent stimulation conditions (here, very slightly positive) and during the two periods when no heat was applied (here, very slightly negative) provide the residual values for evaluating DNIC-like effects.

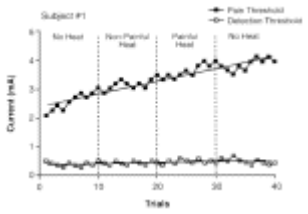

FIG. 1. An example of electrocutaneous detection and pain threshold determinations (40 trials for each staircase) for a fibromyalgia patient. The periods of no concurrent stimulation, concurrent nonpainful heat, and concurrent painful heat are indicated. The regression lines were used for assessment of initial sensitivity (intercept) and adaptation (slope). Analyses for DNIC-like effects were based on the residuals (differences between the staircase value and the regression value at each point).

The residuals were averaged per block of 10 trials at each level. Whereas there were no significant differences in the residuals between the "No Heat" condition in Block 1 and the identical condition in Block 4 (for both the detection and pain thresholds, $p > .05$ in all comparisons [paired *t*-tests, two-tailed] for the fibromyalgia patients and healthy controls), the average of the two blocks was used for further evaluation.

The residuals for the electrical detection and pain thresholds were compared between the "Painful Heat," "Nonpainful Heat," and "No Heat" conditions, and between the fibromyalgia patients and control subjects, by means of an analysis of variance (ANOVA for repeated measures). A general DNIC-like effect would be demonstrated by a significant main effect of the condition factor. A DNIC-like effect that differed between the groups would be demonstrated by a significant interaction between the condition and group factors. Significant main effects between the groups were not anticipated because of the normalization created by the calculation of residuals.

The simple between- and within-group differences were analyzed by means of a priori *t*-tests, with two planned contrasts. For correlational analysis, Pearson's coefficient was computed. One-tailed tests were used throughout, and alpha was set to .05.

## RESULTS TOP

The initial electrocutaneous sensitivity at the detection and the pain threshold levels, as indicated by the intercepts for the individual staircases, was not significantly different between the fibromyalgia patients and the healthy control subjects **(Table 2)**. Similarly, the slope values, taken as the measures of adaptation over the course of the session, did not differ significantly between the groups for both the electrical detection and pain thresholds (see **Table 2**). Hence, the two groups did not differ in electrocutaneous responsiveness or in changes due to repeated stimulation. The slope data did indicate that there was considerable adaptation to repeatedly applied stimuli at the pain threshold level (average increases of 73% in the fibromyalgia patients and of 77% in the healthy control subjects), but almost no adaptation at the detection threshold level (average increases of 11% in the fibromyalgia patients and of 8% in the healthy control subjects).

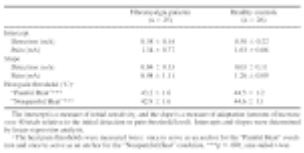

TABLE 2. Means (±SD) of the intercept and slope for the electrical detection and electrical pain threshold staircases as well as the heat pain thresholds

The heat pain thresholds, which served as the reference temperature for subsequent tonic stimulation in Blocks 2 and 3 for each of the groups, were essentially constant when estimates were obtained for their respective "Painful Heat" and "Nonpainful Heat" conditions. However, the heat pain thresholds were significantly lower in the fibromyalgia patients than in the healthy control subjects (see **Table 2**).

The averaged threshold residuals, which eliminate the linear trends due to adaptation, are presented in **Figures 2 and 3**. These show the effects of concurrent tonic thermal stimulation on the electrical detection and pain thresholds. Electrical pain thresholds differed significantly between the "Painful Heat," "Nonpainful Heat," and "No Heat" conditions [$F(2,98) = 3.96$, $p = .011$; see **Fig. 2**]. The group effect and the group × condition interaction were not significant [$F(1,49) = 1.59$, $p = .113$ and $F(2,98) = 1.09$, $p = .170$, respectively]. The latter finding suggested that the condition effect was similar in the two groups. However, the healthy control subjects showed significant differences between "Painful Heat" and "No Heat" ($t = 2.08$, $p = .024$) and between "Nonpainful Heat" and "No Heat" ($t = 2.91$, $p = .001$). For them, both forms of concurrent tonic thermal stimulation produced higher electrical pain thresholds. No comparable condition effect was observed in the fibromyalgia group ($t = 0.49$, $p = .318$ for "Painful Heat" vs. "No Heat" and $t = 1.42$, $p = .084$ for "Nonpainful Heat" vs. "No Heat").

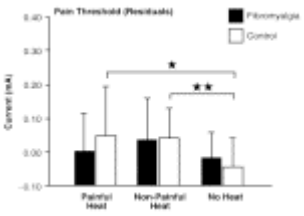


FIG. 2. Electrical pain thresholds (residuals from the regression analysis; means + standard deviation) in the "Painful Heat," "Nonpainful Heat," and "No Heat" conditions for patients with fibromyalgia (n = 25) and healthy control subjects (n = 26). "Painful Heat" and "Nonpainful Heat" differed significantly from "No Heat" only in the healthy control subjects ($p = 0.024$ and $p = 0.001$, respectively, in *t*-tests).

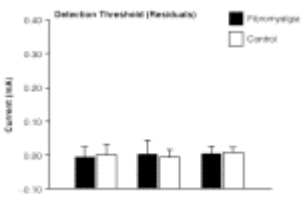


FIG. 3. Electrical detection thresholds (residuals from the regression analysis; means + standard deviation) in the "Painful Heat," "Nonpainful Heat," and "No Heat" conditions for patients with fibromyalgia (n = 25) and healthy control subjects (n = 26). There was no significant difference between the conditions.

The detection thresholds for the electrical pulses were not affected by concurrent tonic thermal stimulation in either of the groups, as evidenced by the lack of significant findings in an ANOVA (see **Fig. 3**). Hence, each of the two intensities of tonic thermal stimulation suppressed electrical sensitivity at painful but not at nonpainful levels, but only in the group of healthy control subjects.

In a correlational analysis, we tested whether the effect of concurrent tonic thermal stimulation on electrical sensitivity was dependent on the intensity of the tonic stimulus. Because the heat pain thresholds served as the reference temperature for the tonic thermal stimulation, correlations were computed separately, for each group, between the heat pain thresholds and the electrical detection and pain thresholds (averaged residuals) in the "Painful Heat" and "Nonpainful Heat" conditions. **Table 3** shows that the heat pain thresholds (and, consequently, the intensities of the painful and nonpainful thermal stimuli) were not significantly related to the electrical detection and pain thresholds during tonic thermal stimulation. Hence, it seems unlikely that the pain-suppressing properties of the tonic thermal stimulus, which was designed to be subjectively equal for all subjects, preferentially affected those with high heat pain thresholds.

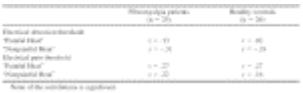

TABLE 3. Pearson's correlation coefficients (r) for the relationship between electrical sensitivity (detection and pain thresholds) and intensity of the concurrent tonic thermal stimulation in the "Painful Heat" and "Nonpainful Heat" conditions

## DISCUSSION TOP

There were three major findings in the present study. First, patients with fibromyalgia were more responsive than healthy control subjects to thermal pain but not to electrical pain at a nontender control point. Second, fibromyalgia patients demonstrated essentially normal adaptation to repeated electrical pain stimulation. Third, and most importantly, concurrent tonic thermal stimulation produced a reduction of electrically induced phasic pain in healthy control subjects but not in patients with fibromyalgia.

The data corroborate, with an altogether different approach, our finding that fibromyalgia patients are hyperresponsive at a nontender control point to heat pain as well as pressure pain.[8] The site of thermal stimulation (dorsum pedis) and the method of pain threshold assessment (method of adjustment) were different from our earlier investigation (inner forearm and method of limits, respectively), suggesting that this is a robust effect. Similarly, the patients and healthy subjects did not differ in electrocutaneous sensitivity at a nontender control point when a staircase method was used for assessment of both the detection and pain thresholds, confirming results obtained with the method of limits. Thus, the concept of pain hyperresponsiveness in fibromyalgia, generalized with respect to the physical nature of the noxious stimulus and the site of stimulation, received only partial support.

The absence of group differences in the degree of adaptation to repeatedly applied electrical stimuli suggests that this kind of pain adaptation is not a critical factor in the pathophysiology of fibromyalgia. Peters and colleagues[22,28] hypothesized that chronic low back pain is caused by deficient "habituation" to continuous or intermittent pain. Whereas their first experiment,[28] using repeatedly applied pressure pain, seemed to corroborate this hypothesis, their second one, using electrical stimuli,[22] did not. Consequently, it is still uncertain whether deficiencies in adaptation or habituation play a critical role in the pathogenesis of chronic musculoskeletal pain.

The degree of adaptation to noxious electrical pulse trains was striking, as was the lack of such an effect for electrocutaneous stimuli at detection levels. Adaptation was likely not itself a DNIC phenomenon. Higashiyama and Tashiro[32] also found adaptation at moderate intensity levels, McLaughlin and Kelly[33] reviewed "systematic and often marked changes" in somatosensory evoked potentials under conditions of repetitive stimulation at various intensities, and Ernst and associates[31] reported a decrease in pain sensitivity for tooth pulp stimulation at both weak and strong stimulus intensities that was not affected by naloxone administration.

The present study did provide evidence to suggest that concurrent tonic thermal stimulation produces pain attenuation in healthy control subjects but not in patients with fibromyalgia. Although it is tempting to declare that tonic pain inhibition is inadequate in patients with fibromyalgia, some qualifying comments are necessary.

First, the nature of the pain suppression in our healthy control subjects remains to be established, because their electrical pain sensitivity was diminished in experimental conditions involving non-noxious tonic heat as well as tonic heat pain. Similar suppressing effects of nonpainful tonic heat, produced by hot water or by a thermode, were observed in a recent study on another group of healthy persons in which the phasic stimulus was noxious heat.[34]

A conventional DNIC effect is supposed to be produced preferentially or exclusively by tonic pain.[19,35] Possibly, nociceptive primary afferents and pathways may be activated by heat at intensities just below the pain threshold. A more cognitive explanation for the pain-suppressing effects of non-noxious heat, seen here for the control subjects, might be that strong (painful and nonpainful) stimuli are capable of directing attention away from pain. Although Plaghki and associates[36] found that distraction acts more on nonpainful perceptions than painful ones, and although we observed no effects of tonic thermal stimulation on nonpainful sensitivity (electrical detection threshold), distraction or other higher-order factors such as the adaptation-level phenomenon[22,37,38,39] may have contributed to the DNIC-like effects demonstrated in our healthy control subjects.

Comparable pain modulation did not occur in the persons with fibromyalgia. This adds further evidence concerning the hypervigilant performance of these patients.[5,8,9] Under conditions of concurrent stimulation, when normal control subjects report a reduction in the level of electrically induced pain (since the current has to be elevated to reach their pain threshold), the fibromyalgia patients' threshold for pain is unaltered.

The tonic thermal stimuli used to induce pain modulation were physically less intense in the patients with fibromyalgia than in the healthy control subjects because the patients had lower heat pain thresholds. Despite the physical differences, however, the stimuli were adjusted relative to the same subjective level, pain threshold for all subjects.

The issue of how to equate noxious tonic stimuli is not specific to our heat pain model; individual differences in pain tolerance restrict the application of physically equal tonic stimuli in other studies of DNIC effects. The recent findings of Guieu and associates[24] suggest that it is the subjective intensity of a stimulus, rather than simply its physical level, that influences the degree of pain inhibition it evokes. They found that a fixed level of pressure to a designated tender point, which was painful for fibromyalgia patients and not painful for healthy individuals, elicited a depression of the amplitude of the nociceptive flexion reflex ($R_{III}$) in some of the former but none of the latter subjects. Hence, the subjective magnitude of a stimulus seems to influence its pain inhibitory properties.

In the present study, when the intensity of the conditioning stimulus was linked to a level of subjective equality, fibromyalgia patients failed to show the pain attenuation seen in healthy control subjects. Studies such as this one show promise of using behavioral methods to elicit primary information about deficiencies in the neural, biochemical, and cognitive bases of pain suppression. Future experiments might seek to replicate and extend these findings using other sites, other tonic and phasic stimuli, other intensities, and other attentional conditions, such as cognitive detractors, to look for additional evidence of deficiencies in DNIC-like or other pain modulating mechanisms in fibromyalgia and in other chronic pain syndromes.

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## Citing Articles TOP

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