Pain 107 (2004) 7–15

PAIN

www.elsevier.com/locate/pain

Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia

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Received 28 January 2003; received in revised form 28 April 2003; accepted 6 May 2003

Abstract

Patients with chronic pain after whiplash injury and fibromyalgia patients display exaggerated pain after sensory stimulation. Because evident tissue damage is usually lacking, this exaggerated pain perception could be explained by hyperexcitability of the central nervous system. The nociceptive withdrawal reflex (a spinal reflex) may be used to study the excitability state of spinal cord neurons. We tested the hypothesis that patients with chronic whiplash pain and fibromyalgia display facilitated withdrawal reflex and therefore spinal cord hypersensitivity. Three groups were studied: whiplash ($n = 27$), fibromyalgia ($n = 22$) and healthy controls ($n = 29$). Two types of transcutaneous electrical stimulation of the sural nerve were applied: single stimulus and five repeated stimuli at 2 Hz. Electromyography was recorded from the biceps femoris muscle. The main outcome measurement was the minimum current intensity eliciting a spinal reflex (reflex threshold). Reflex thresholds were significantly lower in the whiplash compared with the control group, after both single ($P = 0.024$) and repeated ($P = 0.035$) stimulation. The same was observed for the fibromyalgia group, after both stimulation modalities ($P = 0.001$ and 0.046, respectively). We provide evidence for spinal cord hyperexcitability in patients with chronic pain after whiplash injury and in fibromyalgia patients. This can cause exaggerated pain following low intensity nociceptive or innocuous peripheral stimulation. Spinal hypersensitivity may explain, at least in part, pain in the absence of detectable tissue damage.
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Keywords: Pain; Central hypersensitivity; Spinal cord; Nociceptive reflex; Whiplash; Fibromyalgia

1. Introduction

Peripheral injury and/or inflammation, induced experimentally in animals, cause plasticity changes in the central nervous system that result in neuronal hyperexcitability (Woolf and Salter, 2000). This central hypersensitivity causes exaggerated perception of painful stimuli (hyperalgesia) and a perception of innocuous stimuli as painful (allodynia) (Coderre et al., 1993; Dickenson, 1995).

Studies in patients with chronic pain after whiplash injury and with fibromyalgia have demonstrated exaggerated pain responses following sensory stimulation of healthy tissues (Curatolo et al., 2001; Koelbaek Johansen et al., 1999; Moog et al., 2002; Price et al., 2002; Sheather Reid and Cohen, 1998; Sörensen et al., 1998; Staud et al., 2001). This has led to the hypothesis that the central nervous system is hyperexcitable in these patients. Central hypersensitivity could explain exaggerated pain in the presence of minimal and undetectable tissue damage, in that the nociceptive signal is amplified by the hyperexcitable neurons. Furthermore, animal studies suggest that pain could be perceived in the absence of a nociceptive input after induction of irreversible plasticity changes in the central nervous system (Woolf and Salter, 2000).

The possible involvement of central hypersensitivity in chronic pain after whiplash injury and in fibromyalgia is appealing, given the limited knowledge on the mechanisms underlying these pain syndromes. However, in the aforementioned studies on whiplash and fibromyalgia patients, the assessment of central hypersensitivity was based on

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0304-3959/$20.00 © 2003 Published by Elsevier B.V. on behalf of International Association for the Study of Pain.
doi:10.1016/j.pain.2003.05.001

the patients' pain report after sensory stimulation, i.e. it was purely subjective in nature (Curatolo et al., 2001; Koelbaek Johansen et al., 1999; Moog et al., 2002; Price et al., 2002; Sheather Reid and Cohen, 1998; Sörensen et al., 1998; Staud et al., 2001). Therefore, there is still a lack of objective evidence for central hypersensitivity in these patients.

The nociceptive withdrawal reflex is a spinal reflex of the lower extremity that can be elicited by a painful stimulation of a sensory nerve (Willer, 1977). In humans, transcutaneous electrical stimulation of the sural nerve evokes a flexion reflex that can be recorded in the biceps femoris muscle by electromyography (EMG) (Arendt-Nielsen et al., 1994). The minimal intensity of the stimulus that is sufficient to elicit a reflex at a well-defined latency, known as the reflex threshold, usually corresponds to the minimal stimulus intensity that elicits a perception of pain (Chan and Dallaire, 1989; Willer, 1977). A voluntary knee flexion can be excluded when the reflex latency (i.e. the interval between application of the stimulus and muscle contraction) lies below 150 ms (Arendt-Nielsen et al., 1994; Willer, 1984). Therefore, this method can be used as an electrophysiological parameter for quantifying the excitability of spinal neurons (Petersen-Felix et al., 1996).

In the present study we tested the hypothesis that patients with chronic pain after whiplash injury and patients with fibromyalgia have a lower nociceptive withdrawal reflex threshold than healthy subjects. This would provide electrophysiological evidence for hypersensitivity of spinal cord neurons in patients. We selected chronic pain after whiplash injury and fibromyalgia because of the limited knowledge on the mechanisms involved in these pain syndromes.

2. Methods

2.1. Target population

The study was approved by the ethics committee of the University of Bern. All subjects gave written informed consent and received 100 Swiss francs for participating in the study. The patients were informed and agreed that the investigation was performed for research purposes only and that the results would not affect diagnosis, treatment or legal issues concerning their illness.

Three groups were studied: patients with chronic pain after whiplash injury, patients with fibromyalgia and healthy control subjects. To calculate the sample size we considered the figures of a previous investigation, in which the mean threshold to elicit the withdrawal reflex after single electrical stimulation (see threshold to single electrical stimulus) was 16.8 mA and the standard deviation 6.2 (Curatolo et al., 1997). For the present study, we have arbitrarily chosen a value of one-third of the expected mean threshold as the minimum desired difference between patients and controls, i.e. $16.8/3 = 6$ mA. Setting $\alpha = 0.05$ and $\beta = 0.8$, and using a standard deviation of 6.2 mA, a significant difference of 6 mA in reflex threshold among groups would be detected by a sample size of 22 subjects per group in a two-sided hypothesis.

The subjects in the three groups were recruited at the Division of Pain Therapy of the Department of Anesthesiology of the University Hospital of Bern, until the minimum number of 22 completed experiments was reached in all of the groups. Recruitment was extended beyond the minimum number of 22, until this amount was reached in all groups. We recruited 27 whiplash patients, 24 fibromyalgia patients and 29 healthy control subjects. Two patients in the fibromyalgia group decided not to complete the experiment because they felt that the electrical stimuli to be too painful. Thus, 27 whiplash patients, 22 fibromyalgia patients and 29 healthy control subjects completed the study and were analyzed.

Whiplash injury was defined as a musculoligamental strain or sprain of the cervical spine due to hyperextension and/or hyperflexion, without head-contact injury, loss of consciousness, post-traumatic amnesia, fractures or dislocations of the cervical spine (Radanov et al., 1995). Fibromyalgia was defined according to the criteria of the American College of Rheumatology as widespread pain (axial plus upper and lower segment plus left- and right-sided pain) in combination with mild or greater tenderness at 11 or more of the 18 specific tender point sites (Wolfe et al., 1990).

Whiplash patients with neck pain before injury were excluded. Fibromyalgia patients in which symptoms appeared after a trauma were also excluded. Exclusion criteria for both the whiplash and the fibromyalgia groups were: a duration of pain of less than 6 months, pregnancy, any peripheral or central neurological dysfunction and coronary artery disease.

2.2. Descriptive variables

2.2.1. Psychological assessment

The German versions of the NEO-FFI test (Neuroticism, Extraversion, Openness—Five Factor Inventory; Borkenau and Ostendorf, 1993), and of the SCL-90-R (Symptom Check List-90, revised version; Franke, 1995), were used. Both tests are self-report questionnaires.

The NEO-FFI test assesses five personality dimensions (neuroticism, extraversion, openness, agreeableness and conscientiousness) which are considered the major dimensions of the human personality (Costa et al., 1986). This inventory is reliable when retesting over time and is therefore independent of current life circumstances (Costa et al., 1986). It consists of 60 items (12 for each personality dimension). The item analysis yields a score for each personality dimension which is transformed into t-value adjusted to gender (Borkenau and Ostendorf, 1993).

The SCL-90-R is used to assess psychological distress in patients, including patients with chronic pain (Bernstein

et al., 1994; Duckro et al., 1985; Wallis et al., 1997). The SCL-90-R is a multidimensional checklist with 90 items, each describing a physical or psychological symptom. The item analysis yields scores for nine dimensions: somatization, obsession-compulsion, inter-personal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. In addition, a score for the general psychological distress (general severity index) is calculated. The scores are transformed into *t*-values adjusted according to education and gender (Franke, 1995).

The normal range of the scores of both NEO-FFI and SCL-90-R corresponds to *t*-values between 40 and 60. *t*-Values greater than 60 indicates a pathology of the corresponding psychological dimension.

2.2.2. Pain intensity

Patients were asked to quantify the intensity of their pain at rest on a 10 cm visual analogue scale (VAS), where 0 indicates no pain and 10 corresponds to the worst pain imaginable. Patients were also asked to indicate the region of worst pain.

2.2.3. Muscle tenderness

In order to assess muscle tenderness, pain detection and tolerance thresholds were measured with an electronic pressure algometer (Somedic AB, Stockholm, Sweden) (Brennum et al., 1989). The probe had a surface area of 64 mm^2. The pressure was increased from 0 at a rate of 30 kPa/s to a maximum pressure of 1000 kPa.

Pain detection threshold was defined as the point at which the pressure sensation turned to pain. Pain tolerance threshold was defined as the point at which the subject felt pain as intolerable. The subjects were instructed to press a button when these points were reached. The algometer displayed the pressure intensity at which the button was pressed. If the subjects did not press the button at a pressure of 1000 kPa, this value was considered as threshold.

The test was performed at the site of most severe pain in each patient and on the trapezius muscle, right or left (randomly selected) in the control group. The mean of three determinations was used for the data analysis.

2.3. Assessment of central hypersensitivity

2.3.1. General procedure

Electrical stimulation was performed through bipolar surface Ag/AgCl-electrodes filled with electrode gel (inter-electrode distance approximately 2 cm) placed just distal to the right lateral malleolus (innervation area of the sural nerve). EMG reflex responses to electrical stimulation were recorded from the middle of the biceps femoris and the rectus femoris muscles (Ag/AgCl-electrodes). A leg rest was placed under the knee to obtain a 30° semi-flexion. The EMG signal was amplified and filtered (1.5–150 Hz) by a single channel EMG–EEG amplifier (Hellige AG, Freiburg, Germany). Stimulation and recording were controlled and analyzed with the NFRsys software (Noxitest, Aalborg, Denmark).

Initially all of the tests were performed on the subjects for training purposes. When the subjects were familiar with the procedure, the experiment was started. For each of the test modalities described below, three determinations were made and the average of these three measurements was used for the data analysis.

2.3.2. Thresholds to single electrical stimulation

A 25 ms, train-of-five, 1 ms, square-wave impulse (perceived as a single stimulus), was delivered by a computer-controlled constant current stimulator (University of Aalborg, Denmark). The current intensity was increased from 1 mA in steps of 0.5 mA until: (1) a reflex with an amplitude exceeding 20 μV for at least 10 ms in the 70–150 ms post-stimulation interval was detected by the computer program (single stimulus *reflex* threshold); and (2) a pain sensation was evoked (single stimulus *pain* threshold). The program delivered the impulses at random time intervals, so that the subject was not aware of when the stimulus was going to be applied. In this way, we avoided voluntary muscle contraction due to stimulus anticipation and ensured that a spinal reflex was recorded.

2.3.3. Thresholds to repeated electrical stimulation

Repeated stimuli of constant intensity may evoke an increase in the intensity of perception during the repeated stimulation, so that the latter stimuli are perceived as painful (Arendt-Nielsen et al., 1994). This phenomenon is called temporal summation and reflects neuronal integration processes that, most likely, are underlying mechanisms of neuronal excitability (Arendt-Nielsen et al., 1994; Price, 1972). The temporal summation model therefore provides information on central integrative mechanisms of sensory processing. To elicit temporal summation, the stimulus burst used for single stimulus (see above) was repeated five times with a frequency of 2 Hz, at constant intensity (Arendt-Nielsen et al., 1994). The current intensity of the five constant stimuli was increased from 1 mA in steps of 0.5 mA until: (1) an increase in the amplitude of the last two or three reflexes above a fixed limit of 20 μV for at least 10 ms in the 70–150 ms post-stimulation interval was observed (repeated stimulation reflex threshold); and (2) the subjects felt pain during the last two to three of the five electrical bursts (repeated stimulation pain threshold). Whenever subjects felt pain at the first three impulses of the repeated stimulation, this point was considered as repeated stimulation pain threshold.

2.4. Statistical analysis

2.4.1. General aspects

The fibromyalgia group was characterized by a different gender distribution than the other groups, reflecting the well-known higher prevalence of this syndrome in women.

Therefore, in order to obtain control groups that were similar in terms of gender and age distribution to both patient groups, we defined two different control groups for each patient group. For the comparison with the fibromyalgia group, we discarded four of the 29 healthy subjects. These individuals were removed by an investigator who had no access to the experimental results except for age and gender. This was not necessary for the whiplash group as gender and age distribution were similar to the one of the control group. Thus 25 control subjects were compared with 22 fibromyalgia patients and 29 control subjects were compared with 27 whiplash patients in separate analyses. We deliberately renounced comparing the whiplash with the fibromyalgia group because of the differences between the groups in several factors that can affect the results, such as demographic characteristics (including gender), duration of chronic pain, pain intensity at the time of the experiment and psychological profile. These factors would render it problematic to attribute possible differences in the outcome measured to being a whiplash or a fibromyalgia patient, rather than to one or more of the aforementioned confounding factors.

The statistical software used was SigmaStat version 2.03 (Jandel Corporation, San Raphael, CA, USA). A *P*-value less than 0.05 was considered as significant.

2.4.2. Descriptive variables

The groups were compared for age, weight, height, psychological variables and pressure thresholds using the Student's *t*-test. Whenever the variables were not normally distributed we performed the Mann–Whitney rank sum test. Gender was evaluated using the χ^2 test.

2.4.3. Central hypersensitivity

The main outcome variable of the study was the reflex threshold after both single and repeated electrical stimulation. Secondary outcome was the pain threshold after electrical stimulation. Data pertaining to reflex and pain thresholds were analyzed by two-way repeated analysis of variance (ANOVA) on rank, with type of test (single and repeated electrical stimulation) as repeated factor and group as non-repeated factor. Pairwise comparisons were performed by the Tukey test. Additionally, the correlation between reflex and pain thresholds for both single and repeated electrical stimulation was analyzed by the Pearson product moment correlation.

Both reflex thresholds could not be obtained in a fibromyalgia patient, because unbearable pain was felt at current intensities below the reflex thresholds. When recording the repeated stimulation pain threshold, all study participants except three of the whiplash group felt pain only at the last two to three stimulations, thereby showing a true subjective temporal summation response. The aforementioned three whiplash patients were still included in the analysis, the pain threshold during the repeated stimulation being considered.

3. Results

3.1. Descriptive variables

Demographic data and psychological variables are shown in Tables 1 and 2, respectively. Regarding personality traits, all three groups scored within the normal range (i.e. between 40 and 60), despite differences between patients and controls in some dimensions (Table 2). In contrast, both patient groups displayed considerably elevated scores on several dimensions of the SCL-90-R, indicating psychological distress. Particularly high scores were found in the fibromyalgia group.

In the whiplash and fibromyalgia group, the median (25th–75th percentiles) duration of pain was 22 (11–64) and 138 (78–264) months, respectively. The median (25th–75th percentiles) of pain intensity immediately before the experiment was 3.7 (3.2–5.8) and 4.6 (3.0–6.2) cm, respectively.

Data on muscle tenderness as assessed by pressure stimulation are reported in Table 3. Pressure pain detection and pressure pain tolerance thresholds were significantly lower in both patient groups compared with the control groups.

Fifteen whiplash patients, 16 fibromyalgia patients and no healthy control subject were on sick leave in the period when the experiments were carried out.

Table 1
Demographic characteristics

	Whiplash ($n = 27$)	Control ($n = 29$)	*P*-value	Fibromyalgia ($n = 22$)	Control ($n = 25$)	*P*-value
Age (years)	39 (34–48)	46 (29–53)	>0.05	47 (41–54)	47 (35–56)	>0.05
Weight (kg)	65 (60–79)	65 (58–74)	>0.05	76 (55–83)	63 (58–68)	>0.05
Height (cm)	168 (164–172)	170 (163–173)	>0.05	164 (160–170)	168 (163–172)	>0.05
Gender (f/m)	19/8	20/9	>0.05	18/4	20/5	>0.05

Numerical data are presented as medians with 25th and 75th percentiles in parentheses.

Table 2
Psychological variables

Psychological variables	Whiplash ($n = 27$)	Control ($n = 29$)	P-value	Fibromyalgia ($n = 22$)	Control ($n = 25$)	P-value
Personality traits (NEO-FFI)						
Neuroticism	44 (41–54)	40 (37–45)	0.008	54 (48–64)	38 (36–45)	<0.001
Extraversion	50 (45–53)	54 (49–60)	0.011	46 (40–55)	53 (48–58)	0.036
Openness	47 (42–56)	47 (40–52)	> 0.05	47 (41–50)	44 (39–52)	>0.05
Agreeableness	55 (51–62)	57 (51–62)	> 0.05	49 (46–55)	56 (51–62)	0.002
Conscientiousness	57 (54–62)	54 (50–61)	> 0.05	53 (48–59)	56 (51–61)	>0.05
Psychological symptoms (SCL-90-R)						
Somatization	67 (60–79)	42 (36–50)	< 0.001	80 (78–80)	42 (37–51)	<0.001
Obsession-compulsion	62 (52–69)	42 (33–48)	< 0.001	72 (58–80)	42 (38–48)	<0.001
Interpersonal sensitivity	56 (44–62)	42 (35–48)	< 0.001	59 (50–71)	42 (35–49)	<0.001
Depression	58 (50–68)	40 (33–48)	< 0.001	68 (57–80)	42 (32–50)	<0.001
Anxiety	58 (48–65)	40 (36–48)	< 0.001	65 (52–71)	38 (36–48)	<0.001
Hostility	56 (46–64)	45 (36–49)	< 0.001	59 (52–61)	45 (36–49)	<0.001
Phobic anxiety	61 (45–70)	43 (43–45)	< 0.001	58 (52–72)	43 (43–45)	<0.001
Paranoid ideation	48 (41–59)	41 (38–46)	0.010	58 (46–72)	40 (38–46)	<0.001
Psychoticism	49 (46–61)	41 (39–43)	< 0.001	63 (52–71)	41 (39–43)	<0.001
General severity index	61 (53–68)	39 (27–45)	< 0.001	70 (58–80)	42 (32–47)	<0.001

Data are medians (25th and 75th percentiles) of the scores. The higher the score, the worse the impairment of the corresponding dimension. Values below 60 are considered as normal. NEO-FFI, Neuroticism, Openness—Five Factor Inventory; SCL-90-R, Symptom Check List.

3.2. Central hypersensitivity

Reflex thresholds after single and repeated electrical stimulation were significantly lower in both whiplash and fibromyalgia groups than in control groups (Figs. 1 and 2). Median pain thresholds to electrical stimulation were lower in both patient groups compared to control groups, but the differences were statistically significant only for the fibromyalgia group (Figs. 3 and 4).

As expected, we found a positive correlation between pain and reflex thresholds: the correlation coefficient was very high for both single (0.835, $P < 0.001$) and repeated (0.920, $P < 0.001$) electrical stimulation.

4. Discussion

4.1. Main study findings

The stimulus intensity necessary to evoke a spinal reflex is significantly lower in patients with chronic pain after whiplash injury and in fibromyalgia patients than in healthy subjects. This demonstrates a state of hypersensitivity of spinal neurons to peripheral stimulation.

Previous studies on whiplash and fibromyalgia patients analyzed the stimulus intensity necessary to evoke a pain sensation (pain threshold) (Curatolo et al., 2001; Koelbaek Johansen et al., 1999; Moog et al., 2002; Price et al., 2002; Sheather Reid and Cohen, 1998; Sörensen et al., 1998; Staud et al., 2001). In all these studies, the pain threshold was lower in patients than in healthy subjects, which was attributed to a possible hypersensitivity of the central nervous system. However, these studies had two main limitations. First, they did not tell us whether hypersensitivity involves spinal cord neurons or not. Second, because of the pure subjective nature of the measurements, a voluntary or even unconscious symptom amplification without neurobiological hyperexcitability changes of the central nervous system could not be ruled out. For instance, malingering and secondary gain mechanisms could be determinants of such symptom amplification.

Table 3
Muscle tenderness (pressure pain thresholds)

	Whiplash ($n = 27$)	Control ($n = 29$)	P-value	Fibromyalgia ($n = 22$)	Control ($n = 25$)	P-value
Pain detection threshold (kPa)	192 (131–313)	497 (386–662)	<0.001	125 (95–221)	497 (386–660)	<0.001
Pain tolerance threshold (kPa)	338 (243–504)	779 (652–942)	<0.001	202 (152–277)	779 (652–898)	<0.001

Data are medians (25th–75th percentiles). In patients, the test was applied at the site of strongest pain. Whiplash patients were tested at the following sites: 22 on the neck and 5 on the shoulder. Pressure was applied at the following sites on fibromyalgia patients: 7 on the shoulder, 3 on the wrist, 3 on the lower back, 3 on the biceps brachii muscle, 2 on the neck and 1 each on the elbow, forearm, thigh and hip. The control subjects were all tested on the trapezius muscle (side chosen by randomization).

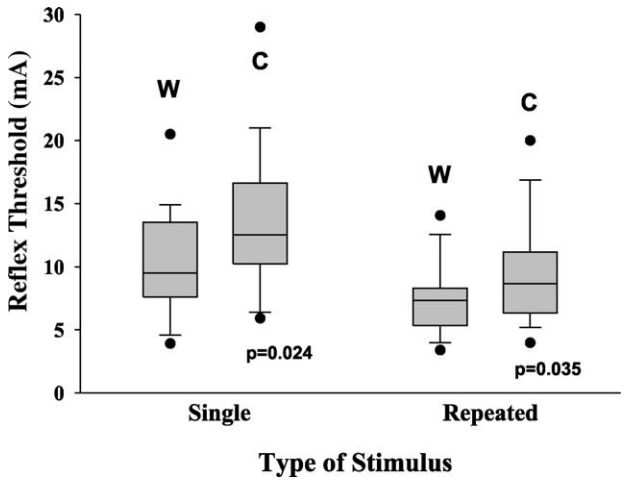

Fig. 1. Reflex threshold in whiplash patients as compared to the control group. W, whiplash group; C, control group. *X*-axis: 'single' represents a single electrical stimulus threshold; 'repeated', the repeated electrical stimulus threshold (five stimuli at 2 Hz). Data are presented as median, 10th, 25th, 75th and 90th percentiles. The black dots represent the values that lie outside the 10th and 90th percentiles.

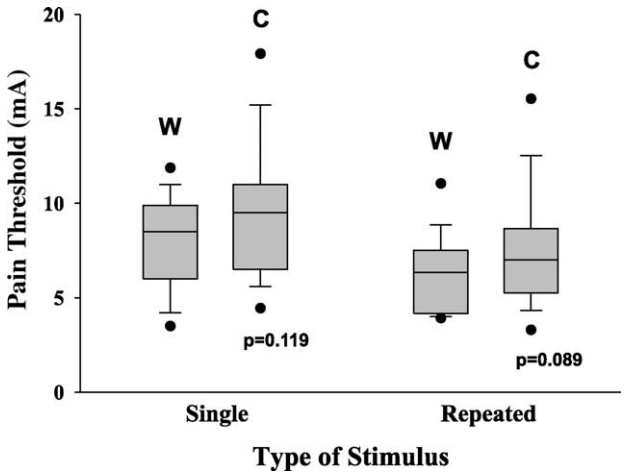

Fig. 3. Pain threshold in whiplash patients as compared to the control group. W, whiplash group; C, control group. *X*-axis: 'single' represents a single electrical stimulus threshold; 'repeated', the repeated electrical stimulus threshold (five stimuli at 2 Hz). Data are presented as median, 10th, 25th, 75th and 90th percentiles. The black dots represent the values that lie outside the 10th and 90th percentiles.

Thus the present study is the first one clearly demonstrating that spinal cord neurons are sensitized in chronic pain after whiplash injury and in fibromyalgia. Because we delivered the stimuli at random time intervals and measured the latency of the EMG response, we could rule out voluntary symptom amplification as determinant of central hypersensitivity.

In addition to reflex measurements, we assessed the pain thresholds to electrical stimuli. We found lower median pain thresholds in whiplash and fibromyalgia patients as compared to healthy subjects. Interestingly, the differences in pain thresholds between whiplash patients and controls did not reach statistical significance, which suggests that reflex measurements may be more sensitive than pain threshold measurements for detecting central hypersensitivity.

The presence of spinal cord hypersensitivity in these two very different pain syndromes suggests that this phenomenon may be present also in other chronic musculoskeletal pain states.

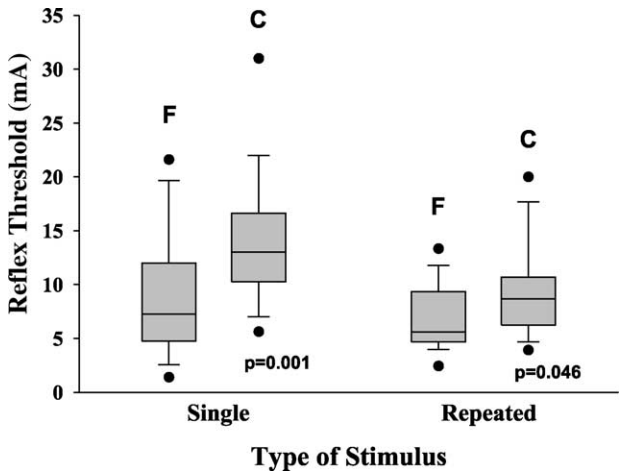

Fig. 2. Reflex threshold in fibromyalgia patients as compared to the control group. W, whiplash group; C, control group. *X*-axis: 'single' represents a single electrical stimulus threshold; 'repeated', the repeated electrical stimulus threshold (five stimuli at 2 Hz). Data are presented as median, 10th, 25th, 75th and 90th percentiles. The black dots represent the values that lie outside the 10th and 90th percentiles.

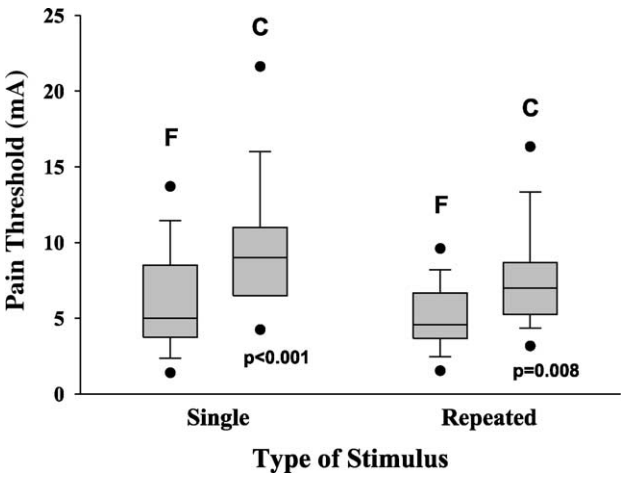

Fig. 4. Pain threshold in fibromyalgia patients as compared to the control group. W, whiplash group; C, control group. *X*-axis: 'single' represents a single electrical stimulus threshold; 'repeated', the repeated electrical stimulus threshold (five stimuli at 2 Hz). Data are presented as median, 10th, 25th, 75th and 90th percentiles. The black dots represent the values that lie outside the 10th and 90th percentiles.

4.2. Interpretation

Exaggerated pain after peripheral stimulation is common in whiplash and fibromyalgia patients (Sheather Reid and Cohen, 1998; Sörensen et al., 1998). Theoretically, peripheral mechanisms can account for such a pain hypersensitivity. Tissue damage and inflammation produce a variety of local biochemical events (Rang et al., 1991) that sensitize the peripheral receptors (Treede et al., 1992) and may activate normally inactive nociceptors (Schmidt et al., 1995). Peripheral inflammation induces a gene expression in the dorsal root ganglion resulting in an increased synthesis of peripheral receptors (Michael and Priestley, 1999). These events mediate primary hyperalgesia, whereby a reduced threshold for eliciting pain within the injured area can be detected.

Peripheral tissue damage is not detected in many patients with chronic pain after whiplash injury (Radanov et al., 1995), although the available diagnostic tools may fail to identify the peripheral source of pain (Bogduk and Teasell, 2000). For fibromyalgia, no evidence for peripheral tissue damage, as explanation for widespread pain, exists. We applied the stimulation at tissues where no evident tissue damage was present. Moreover, the electrical stimulation bypasses peripheral receptors and activates directly the nerve fibers (Handwerker and Kobal, 1993). Therefore, the low reflex and pain thresholds observed in our study do not result directly from peripheral sensitization.

In animal preparations, tissue damage induces profound plasticity changes in the spinal cord that result in increased responsiveness to peripheral stimulation (Woolf and Salter, 2000). This could also occur in patients and explain our findings. An important question is why hypersensitivity is observed at tissues that are not injured and distant from the site of pain, i.e. the leg. An expansion of receptive fields (cutaneous area innervated by a single neuron) of individual dorsal horn neurons is documented (McMahon and Wall, 1984). As a result, a peripheral stimulus activates a higher number of dorsal horn neurons and hyperalgesia may also be evoked in healthy areas surrounding the injured region. However, this is an unlikely explanation for hypersensitivity after lower limb stimulation in patients with, for instance, neck pain. Inflammation produces expression of cyclooxygenase-2 (COX-2) in the spinal cord, which leads to prostaglandin production and neuronal hyperexcitability (Ichitani et al., 1997). Importantly, COX-2 expression is not confined to the neural structures connected to the site of inflammation, but is observed in the whole spinal cord and in supraspinal centers (Samad et al., 2001). This may explain widespread spinal cord hyperexcitability after inflammation and tissue damage. Activation of glial cells has also been found to be involved in widespread hyperexcitability of spinal cord neurons (Watkins et al., 2001). This could be an additional explanation for generalized hyperexcitability.

An additional puzzling question is why hypersensitivity is observed in the absence of evident tissue damage. Animal research has convincingly shown the occurrence of potentially irreversible changes in the central nervous system after tissue damage, such as expression of gene products, destruction of inhibitory interneurons and aberrant excitatory connections (Woolf and Salter, 2000). These changes might persist after injury has healed, thereby explaining persistent pain. Moreover, absence of evident tissue damage does not necessarily mean that there is no tissue damage. For instance, the zygapophysial joints have been identified as a frequent source of pain after a whiplash injury, even when clinical and radiological investigations do not show specific lesions of these joints (Lord et al., 1996). These data lead to the hypothesis that tissue damage, recognized or not by the available diagnostic methods, induces persistent hyperexcitability of spinal cord neurons of patients that is involved in persistent pain complaints. The underlying mechanism may be either a sustained central facilitation by nociceptive input from an unrecognized peripheral focus or spinal cord plasticity changes that persist after resolution of tissue damage.

Elevated levels of substance P and excitatory amino acids have been found in the cerebrospinal fluid of fibromyalgia patients (Larson et al., 2000; Russell et al., 1994). The origin of this finding is unclear, but these substances may cause generalized spinal cord hyperexcitability. Whether similar biochemical changes in the cerebrospinal fluid are present also in whiplash patients is unknown.

Supraspinal mechanisms may be an additional explanation for spinal cord hyperexcitability and persistent pain. Spinal cord hyperexcitability elicited by trauma or inflammation is influenced by descending facilitatory and inhibitory pathways (Dubner and Ren, 1999). Consistent with previous studies (Curatolo et al., 2001; Offenbaecher et al., 1999; Wallis et al., 1997), we found that patients had psychological distress. In an early study on healthy volunteers, the nociceptive reflex was inhibited by a mental task but facilitated by a stress induced experimentally (Willer et al., 1979). In contrast, a powerful inhibition of the nociceptive reflex after experimentally induced repetitive stress was observed in another investigation (Willer, 1980). The influence of supraspinal mechanisms on spinal nociceptive processes is also supported by the reduction in the nociceptive reflex that was induced by hypnosis in healthy volunteers (Zachariae et al., 1998). In a recent investigation, catastrophizing was found to correlate with the intensity of reported pain after electrical stimulation, but not with the threshold to elicit the nociceptive reflex in healthy volunteers (France et al., 2002). This suggests that catastrophizing may enhance pain perception, but may not affect the spinal processing of nociceptive stimuli. Therefore, catastrophizing would involve pure supraspinal mechanisms, rather than impairing the descending modulation of spinal excitability.

The above data indicate a possible influence of psychological factors on spinal nociceptive processes, whose mechanisms are complex and poorly understood.

In patients, the influence of supraspinal mechanisms on the spinal cord reactivity to sensory stimulation is probably different from the one observed in healthy volunteers and certainly more complex. There is no investigation analyzing the influence of chronic psychological distress on spinal cord excitability in the absence of pain. Therefore, it is difficult to evaluate whether and to what extent psychological factors played a role in the facilitation of the nociceptive reflex that we observed.

Particular genotypes of the serotonin gene in fibromyalgia patients are associated with higher levels of depression, psychological distress and pain (Bondy et al., 1999; Offenbaecher et al., 1999). Given the involvement of serotonin in descending modulation (Li and Zhuo, 2001), one can hypothesize that genetic factors account for both psychological disturbances and imbalance of descending pain modulation, the latter mechanism leading to enhanced pain reactivity. The hypothesis that the psychological distress typical of chronic pain conditions is a determinant of spinal cord hyperexcitability via imbalance of descending modulatory mechanisms is interesting and deserves further investigation.

4.3. Conclusions

Using an objective assessment procedure, we found spinal cord hyperexcitability in chronic pain after whiplash injury and in fibromyalgia. This finding can explain exaggerated pain following low intensity nociceptive stimulation arising from areas of minimal and undetectable tissue damage or pain after innocuous sensory stimulation.

The study does not allow conclusions on the causes of spinal cord hyperexcitability. Plasticity changes in the spinal cord excitability induced by peripheral mechanisms, genetically driven biochemical alterations in the neurotransmitter system and imbalance of descending modulatory pathways due to psychological factors may be responsible for the neuronal hypersensitivity. Independent of the cause, the study demonstrates that both patient groups have neurobiological changes that are likely to alter the spinal nociceptive processing of peripheral stimuli.

Acknowledgements

We thank the Scientific Funds of the Department of Anesthesiology of the University of Bern (Switzerland) and the Danish Technical Research Council for providing the financial support.

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