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Pressure Pain Threshold Changes After Repeated Mechano-Nociceptive Stimulation of the Trapezius Muscle: Possible Influence of Previous Pain Experience

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Abstract: We examined the relation between repeated noxious pressure over the trapezius muscle and changes in pressure pain thresholds (PPTs) in a before-after trial design. A conditioning series of 30 mechano-nociceptive stimuli was applied manually with a handheld algometer probe, and PPTs were measured over 1 trapezius muscle (skin anaesthetized) in 27 healthy women before and after the intervention. With a mean stimulation rate of 0.40 Hz and a mean nociceptive stimulation intensity of $1.78 \times$ Threshold, subjects were found to systematically react with a change in PPT, either a decrease or an increase. Normalized data, transformed into mean unidirectional PPT differences, showed statistically highly significant changes after intervention. The relative risk of reacting with lowered PPTs on noxious stimulation was 3.7 times higher for subjects who had not given birth to children than for subjects who had given birth to 1 or several children ($P < .046$). When 11 subjects were tested at a second session, a clear correlation of PPT reactions ($r = 0.527$; $P < .001$) was found. In summary, repetitive mechano-nociceptive stimulation of the trapezius muscle in healthy females evokes moderate and temporary changes in PPT that last for at least 35 minutes after cessation of stimulation.

Perspective: A possible development of the response with transiently decreased PPTs into a model for human muscle pain is an intriguing possibility, since other models usually involve the introduction of chemical or thermal agents in the muscle, but this must await further research.

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Key words: Tenderness, pain threshold, women, human model, muscle.

It has been shown that regional soft tissue pain is related to repetitive or static work,^{23,30} and it is usually assumed to be muscular in origin. The pathophysiological mechanisms behind this very common phenomenon are not as yet properly understood. Peripheral sensitization of nociceptors has long been suggested as 1 possible causative mechanism¹¹ and has been presumed to be related to metabolic alterations in contracting muscles.¹⁸ In some studies, repetitive work has been found to cause

a decrease in the pressure pain thresholds (PPTs) over muscles involved in the task performed.^{26,31} Peripheral pathological changes, for example, injury, inflammation, or changes in muscle blood flow causing peripheral sensitization of nociceptors and hyperreflexia, have been suggested as possible precipitators.^{28,29} However, biopsy specimens from muscles exposed to long-term static work loads do not show specific pathoanatomical changes.¹⁷ Recently, however, an increased number of ragged-red fibers, presumed to indicate a disturbance in mitochondrial function, were described in tender trapezius muscles among female cleaners.¹⁶

Interestingly, animal experiments have demonstrated that repetitive activation of nociceptive C fibers with either electrical or natural stimuli may give rise to a temporary increase in the transmission in nociceptive pathways.^{21,22,27,36,37,46} A central sensitizing mechanism for the development of long-standing musculoskeletal pain in animals⁴³ and in humans may also exist, at least for

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temporomandibular disorders²⁴ and for fibromyalgia.^{35,44} There is now some evidence from studies of tension-type headache⁴⁵ that tenderness may also have a central mechanism.

We have recently demonstrated in healthy women and in women with chronic shoulder pain that a unilateral standardized static contraction in shoulder muscles for as long as possible leads to a lasting bilateral increase and not a decrease in PPTs.^{33,34} At the same time, we found that the muscle fatigue evoked by the endurance test recovered much faster than the change in PPTs, indicating little or no relation between the peripheral metabolic load in the muscle and the PPT changes. These findings might be explained by the activation of central nervous antinociceptive mechanisms, for instance, mediated through bulbospinal descending pathways.^{14,44,47} In this context, it is interesting to note that a major physiological role of the descending bulbospinal diffuse noxious inhibitory control (DNIC) system^{19,20} is believed to produce hypoalgesia during delivery. It has been found by Gintzler and Komisaruk⁶ in animals and Whipple and Komisaruk⁴⁸ in humans that these systems are activated also by innocuous mechanical stimulation of the cervix uteri. Could it be that the experience of such a profound physiological activation facilitates an activation of the DNIC system when nociceptive stimuli are encountered later in life?

The aim of this study was to further explore whether sensory stimuli can induce changes of sensation in humans. We have now explored whether repetitive noxious pressure over the trapezius muscle on 1 side can give rise to lasting changes in PPTs in the same region of healthy women. In addition, all subjects were asked about their menstrual cycle, their use of hormonal contraceptives, and about their number of childbirths, since it has been maintained that the menstrual cycle may influence PPT measurements.² Preliminary reports have been given.^{41,42}

Methods

Subjects

Twenty-seven female hospital or university employees without ongoing pain (average age, 38 years; range, 22 to 61 years) agreed to take part in our study. Some of them had previously participated in an earlier study³³ of PPTs after a static muscle endurance test. The professions of the subjects were physiotherapy (n = 13), nursing (n = 7), secretarial work (n = 3), social therapy (n = 2), occupational therapy (n = 1), or hospital cleaning (n = 1). In a questionnaire, all the subjects were asked about pain medication; about arm work, regular exercises, or participation in aerobics sessions; about previous injury in the neck-shoulder region; about week of menstrual cycle (menses = week 1), use of hormonal contraceptives, ongoing pregnancies, and number of children; and about smoking habits.

The exclusion criteria were (1) ongoing pain from the musculoskeletal system; (2) analgesic or antidepressive

medication; (3) ongoing pregnancy; and (4) tenderness in the trapezius muscles.

Twenty-four subjects were nonsmokers, 2 smoked 5 to 20 cigarettes a day, and 1 subject used snuff. Six subjects used hormonal contraceptives and 2 were in the menopause. Twenty-two participants were right-handed and 5 were left-handed. Verbal and written information about the procedure was given both before and at the time of the test, and all subjects gave their informed consent before inclusion in the study. The study was approved by the Human Ethics Committee of Lund University.

PPT Measurements

An electronic pressure algometer (Somedic Sales AB, Hörby, Sweden) was used to measure PPTs.^{10,32} This apparatus consists of a gun-shaped handle with a pressure-sensitive strain gauge at the tip and is connected to a power supply, an amplifier, and a display unit. The contact area in the present study was 8 mm in diameter, and the probe tip was covered with a 1-mm-thick rubber pad to minimize irritation of the skin. The pressure was applied perpendicularly against the skin over marked points (see below) and was increased at a standardized speed of 50 kiloPascals/s (kPa/s). A scale on the display helped the investigator to keep the rate of the pressure increase constant. The subjects were instructed to press a signal button when the sensation of "pressure" changed to "pain or discomfort."⁴ The registered pressure threshold measured in kiloPascals was then frozen on the display unit. The instrument was calibrated at the start of the series with the 8-mm probe, and the zero level was balanced before each measuring session. All measurements were performed by the same person. The technique has been found to have a satisfactory repeatability.³²

Protocol

All 27 subjects followed the present test protocol once. In addition, it was possible to test 13 of the subjects at a second session, 1 to 2 weeks later. Two hours before the experiment, the subject was scheduled for test preparations. The subjects were comfortably seated in a chair with a low support for the back and with a pillow on the lap for arm support. Three evenly distributed recording points were palpated and selected along a straight line from the spinous process of the seventh vertebra over the descending part of the trapezius muscle to the lateral edge of the acromion on the dominant side and marked with a felt pen (the same points as in our earlier studies³²⁻³⁴).

To exclude a cutaneous sensory input in the present study, the 2 medial points, representing the main part of the descending trapezius muscle, were covered with 4% lidocaine cream (EMLA; AstraZeneca, Wilmington, DE⁵) in an occlusive bandage (size, 60 × 70 mm) for 90 minutes. While waiting for the EMLA cream to be absorbed, the subjects returned to their regular work. When they came back, the bandage was removed and the cutaneous sensibility to pinprick and to light touch was tested

for its absence in the experimental area immediately before the PPT measurements. Two test trials on a single point over the contralateral trapezius muscle were performed to familiarize the subject with the PPT measurement procedure.

At the start of the experiments (5 minutes before intervention; Fig 1: “–5min”), the PPTs were measured 3 times at 30-second intervals at each of the marked points, starting medially. The point in the anaesthetized area showing the most stable PPT in this initial measurement (usually the medial point) was then selected for further study. The PPTs of this point were measured again 3 times with 30-second intervals at time “0 min.” Thereafter, this point was subjected to an intervention in the form of a noxious conditioning stimulation, consisting of a series of mechano-nociceptive stimuli at an intensity of at least 1.5 times threshold (T; equals the mean PPT determined from 3 PPT measurements just before the intervention at time “0 min”). If this value did not reach 300 kPa, a minimum stimulation pressure of 300 kPa was still used to ascertain a nociceptive stimulation procedure (cf).³²

The stimuli were applied manually 30 times in a perpendicular fashion on the measured point with the handheld algometer probe at the maximum repetition rate possible (the display of the Somedic unit has a short delay before resetting to zero). The duration of the conditioning stimulation was registered. At the end of the conditioning stimulation, each subject estimated her pain intensity on an ordinary 100-mm visual analogue scale (VAS)^{3,38} to ensure that a painful stimulation had indeed taken place. The conditioning stimulation was followed by new series of 3 PPT measurements at “0.5 min” and thereafter at every fifth minute for 20 to 35 minutes after cessation of the intervention. In total, 7 to 10 PPT measurements (each repeated 3 times) were made over the conditioned muscle point. It was not considered possible to include testing of other points in the present study because of the time restraints imposed by the repeated PPT measurements. The examiner performing the conditioning stimulation was blinded to the family situation of the subjects.

Statistics

The results are presented for each individual as the mean of the 3 recorded PPT values at 30-second intervals at each given point in time, both as absolute values and as normalized values in relation to those at “0 min.” Thereafter, normalized unidirectional PPT differences were calculated at all points in time, and 2-way ANOVA for repeated measures with Dunnett’s post hoc test was used for before-after analysis (Instat) between “–5min” and other points in time. Single missing values at 20 to 35 minutes were replaced by “last value carried forward.” Further, Spearman’s test for the correlation between the PPT measurements at the first and the second test sessions for 11 subjects was used (2 subjects excluded due to

outlier data values) as well as Student’s 2-tailed unpaired *t* test and Fisher’s exact test for comparisons between groups (Instat). A significance level of $P \leq .05$ and a 95% confidence interval (CI) were used.

Results

Effects of Repetitive Noxious Stimulation

The duration of the conditioning stimulation was measured and found to be on the average 76 (CI: 72 to 80) seconds. The actual mean nociceptive stimulation intensity was found to be 1.78 (CI: 1.60 to 1.97) \times T, and the mean stimulation rate was 0.40 (CI: 0.36 to 0.42) Hz. Interestingly, the subjects were found to systematically react with PPT changes after conditioning nociceptive stimulation (arrows in Fig 1), either as a decrease ($n = 13$) or as an increase ($n = 14$) in PPTs (Fig 1: A, absolute values, and B, normalized values in relation to those at “0 min”). When the normalized data were transformed into unidirectional PPT differences (Fig 1C), there was a statistically highly significant difference between the mean PPT before (“–5 min”) and those after intervention (ANOVA, $P = .0002$, for Dunnett’s post hoc test, see Fig 1C). Normalization in relation to the values at “–5 min” produced similar results (ANOVA, $P = .0022$).

Repeated Observations After Conditioning Noxious Stimulation in the Same Subjects

With the unexpected finding of 2 opposite reaction patterns (Fig 1B), we managed to retrieve reliable data from a second test, carried out within 7 to 10 days, in 11 subjects. The test procedure was identical to the 1 used at the first test. No significant differences were noted in conditioning stimulation parameters between the 2 test sessions. The poststimulatory mean VAS pain estimate at the second test session was 58 (95% CI: 43 to 73) mm, not statistically different from that at the first test session (48; 95% CI: 42 to 54 mm). There was a significant correlation between the absolute PPTs (kPa) measured in the same subject at corresponding times in the first and second sessions after a series of noxious stimuli (Fig 2A, $r = 0.527$; $P < .001$; Spearman) as well as between their normalized differences (Fig 2B, $r = 0.339$; $P < .002$; Spearman). The mean difference between the 2 measurement sessions at the same point in time from the same individual was 5.9 (CI: –6.0 to +17.8) kPa.

Relation to Menstrual Cycle and to Childbirth

Among the present subjects, there was a tendency for those tested in the early menstrual cycle to react with a decrease in PPT on noxious stimulation and for those tested in the late menstrual cycle to react with an increased PPT, but the difference was not statistically significant (Fisher’s exact test). However, when it came to having given birth to children or not, the relative risk of reacting with lowered PPTs on noxious stimulation was 3.7 times higher for those who had not given birth ($n =$

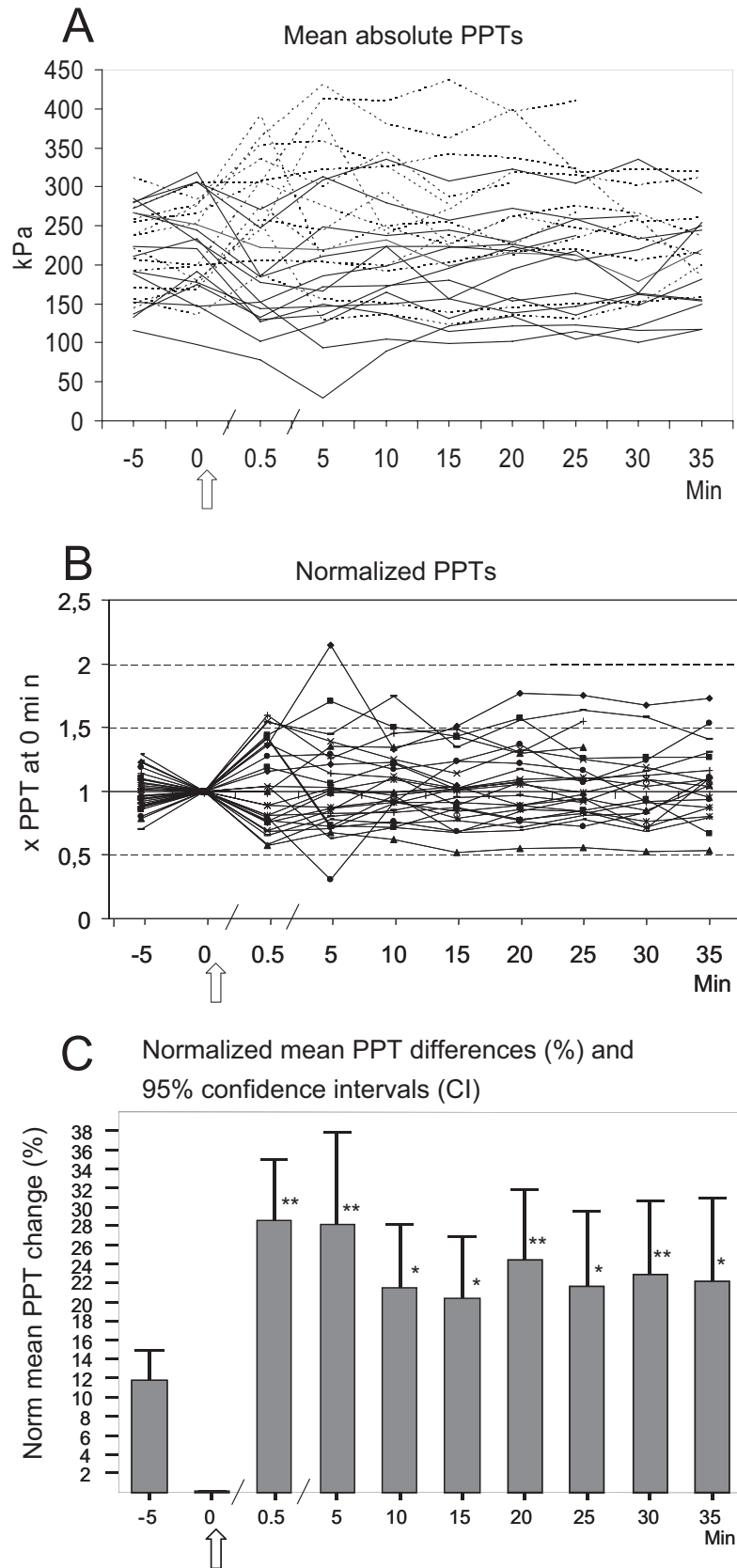


Figure 1. **A**, mean absolute PPT values (kPa), and **B**, normalized PPT values (%) in relation to those at "0 min" for each subject before and after conditioning stimulation at "0 min" as described in text ($n = 27$). Note that the points in time cited after the stimulation do not include the duration of the conditioning stimulation (mean, 76 seconds). In **A**, interrupted lines denote a PPT up reaction and uninterrupted lines denote a PPT down reaction after conditioning stimulation. **C**, normalized mean PPT differences (%) and error bars showing 95% confidence intervals (CI) before and after conditioning stimulation at "0 min" as described in text ($n = 27$). Open arrow indicates conditioning stimulation. Oblique lines on the x-axis denote change of time scale. * $P < .05$, ** $P < .01$ (level of significant difference between groups; Dunnett's test).

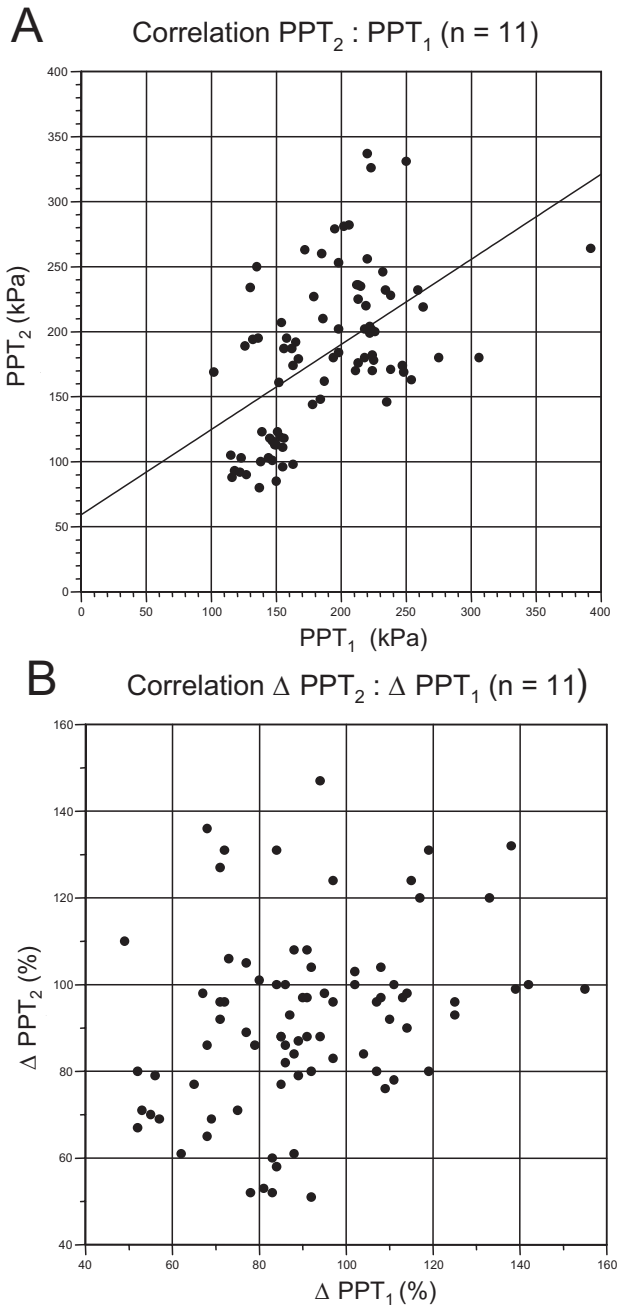


Figure 2. **A**, Correlation between PPTs (in kPa) measured at identical points in time after conditioning stimulation on two different occasions for 11 of the subjects, nine of whom displayed a decrease in PPTs. PPT_1 (x-axis) – first measurement; PPT_2 (y-axis) – second measurement. Each subject contributed 7 to 9 values. **B**, Correlation between normalized differences (% in relation to the PPT at time “0 min”, control). ΔPPT_1 (x-axis) – first measurement; ΔPPT_2 (y-axis) – second measurement.

10) to children than for those who had given birth ($n = 17$) to 1 child or several children ($P < .046$; Fisher’s exact test).

Furthermore, when the PPT temporal patterns were divided into those who had no children versus those who had given birth to 1 or several children (Fig 3), there was a clear tendency to react with a lowered PPT pattern in those without the experience of childbirth and the op-

posite in those who had given birth (significantly different between groups at “+20 min” and at “+25 min”; $P < .05$; Student’s t test), even though the within-group comparisons were not significant (ANOVA).

There were no significant differences between these groups with respect to frequency or intensity of conditioning stimulation and age (Student’s t test) or smoking habits, point in time of menstrual cycle, previous trauma to the shoulder region (2 subjects in each group), or regular muscle exercise (7 subjects in each group; Fisher’s exact test).

Discussion

In the present study, we unexpectedly found 2 types of PPT changes on identical repetitive noxious mechanoreceptive stimulation of a shoulder muscle in a group of healthy women. One is a decrease and 1 is an increase in the PPT, both discernible for the whole observation period (35 minutes) after conditioning stimulation (Fig 1).

The decrease is a clinically expected response on muscle irritation, for example, tenderness. From recordings of identified muscle nociceptors,²⁵ we now know that stimulation of slow, that is, small unmyelinated nerve fibers (groups III and IV) from the peroneal muscle in humans, evokes the experience of pain. From animal experiments, it is also known that stimulation of thin nociceptive nerve fibers may evoke an increase in excitability of the nociceptive systems in the spinal cord in the form of “windup” at the first synapse^{27,37} and sometimes selectively from deep afferents.⁴⁶ Other studies of such phenomena in animals^{21,22} and in humans¹³ have also implicated long-term potentiation. A similar phenomenon has been described in healthy humans after trauma¹² and in cases of fibromyalgia.³⁵ Since we ap-

Mean PPT in relation to previous pain experience ($N = 27$)

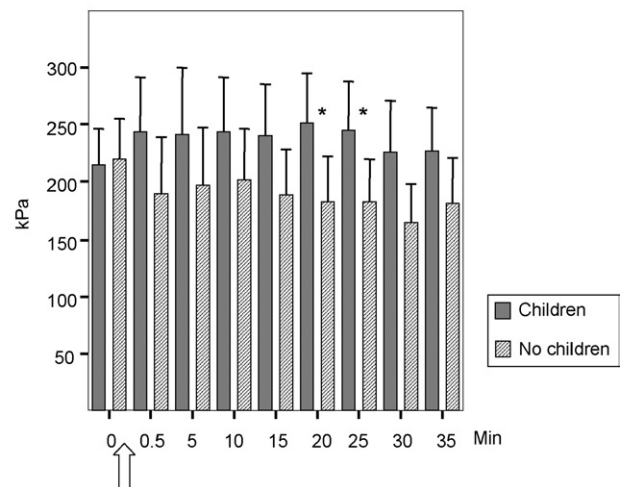


Figure 3. Mean temporal PPT profile after repeated mechanoreceptive stimulation in relation to previous intense pain experience (subjects who had childbirth experience; $n = 17$, vs those who had not; $n = 10$). Open arrow indicates conditioning stimulation. *Significant difference between groups, $P < .05$. Error bars indicate 95% confidence intervals (95% CI).

plied the conditioning stimulation in the same point as we studied for excitability changes, we cannot, however, exclude a peripheral component in the present findings.

The increase in pain thresholds observed in some subjects here is similar to the lasting and widespread PPT increases seen after a static muscular endurance test that we have observed previously.^{33,34} We suggested that this was due to a central antinociceptive mechanism activated by muscle exertion. This mechanism may also have functioned in some subjects in the present test situation. Systems with such properties are well known and can include descending bulbospinal pathways.⁴⁰ The most frequently studied system, the DNIC, is known to be activated by noxious stimuli on large parts of the body and to influence spinal nociceptive transmission in the whole spinal cord.^{19,20} The observed increase of pain intensity in the present subjects, well within the range of "moderate pain" in validation studies of the VAS scale,³ could have activated DNIC-like mechanisms in some subjects, evoking the observed PPT increases.^{35,39,44} Kosek and Ordeberg¹⁵ have also found signs of activation of this system by clinical pain in humans.

The factors determining whether an individual reacts with an up or a down response could be related to different life experiences or to the present life situation. The fact that we found a reasonably strong correlation between the first and second responses indicates that a substantial change over time does not occur over 1 to 2 weeks, however.

Interestingly, whether a subject had given birth to children or not significantly influenced the type of response pattern, in that subjects with children responded more often with increased PPTs, whereas those without children responded with lowered PPTs. In accordance with this finding, Hapidou and DeCatanzaro⁹ have reported that a painful childbirth experience is sufficient to raise the cold-pressor pain thresholds in a group of parous

women. The descending bulbospinal DNIC system is believed to produce hypoalgesia during delivery and has additionally been demonstrated, both in animals⁶ and in humans,⁴⁸ to be activated by innocuous mechanical stimulation of the cervix uteri. Therefore, the DNIC may have been activated extensively in women who have given birth, both by mechanical (innocuous and/or noxious) stimulation of the cervix uteri and by noxious stimulation of the vagina and other parts of the birth canal.

It might be argued that the 2 types of PPT response patterns found are merely variations around a mean. However, we have previously demonstrated that PPT recordings over time are stable and that the technique has a high repeatability.³² Moreover, the observation that a division of our subjects, based on an independent factor, those with and without the experience of child birth, tends to separate the subjects according to their different PPT reactions speaks against that our findings would represent a random variation. Second, when the intervention is repeated over time, the resulting PPT changes correlate well.

In summary, repetitive mechano-nociceptive stimuli given to the trapezius muscle in healthy women evoke moderately long-lasting changes in PPTs. A possible development of the response with decreased PPTs into a model for human muscle pain is an intriguing possibility, since other models usually involve the introduction of chemical or thermal agents in the muscle,^{1,7,8} but this must await further research.

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