

Gender differences in electrical pain threshold responses to transcutaneous electrical nerve stimulation (TENS)

Irène Lund^{a,*}, Thomas Lundeberg^b, Jan Kowalski^a, Elisabeth Svensson^c

^a Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm SE-17177, Sweden

^b Rehabilitation Medicine Clinic, Karolinska University Hospital, Stockholm, Sweden

^c Department of Business, Economics, Statistics and Informatics, Örebro University, Sweden

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Abstract

Gender differences in pain perception have been frequently discussed, but the documented gender-related pain-alleviating effects of non-pharmacological methods are sparse. In this study we aimed to investigate changes in electrical sensory thresholds and electrical pain thresholds, in response to high frequency transcutaneous electrical nerve stimulation, TENS, for 20 min in healthy women ($n = 29$) and men ($n = 29$). The thresholds were assessed pre-, during-, and post-TENS. The pattern of change in thresholds was evaluated with a rank-based statistical method regarding the level of systematic change, expressed as relative position (RP) and additional individual changes, expressed as relative rank variance (RV), with its 95% confidence intervals. Equal levels of systematic changes towards increased electrical sensory thresholds were seen in women and men post-TENS (RP, 0.35; 95% CI, 0.07, 0.63, and RP, 0.36; 95% CI, 0.17, 0.53, respectively). At the same point of time, systematic changes towards increased electrical pain thresholds were only seen in women (RP, 0.43; 95% CI, 0.27, 0.60), while they were unchanged in men (RP, -0.01 ; 95% CI, -0.13 , 0.10). Significant additional individual variations were found in the women's responses of assessed electrical sensory and pain thresholds but not in the men's. It is concluded that both women and men responded with a significant increase of the electrical sensory threshold to high frequency TENS, but only women responded with increase of the electrical pain thresholds. The individual variation of the responses was greater in the women than in the men.

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Different perceptions of nociceptive stimuli in women and men have long been the subject of speculation and investigation. In women, painful experimental stimuli are generally reported with signs of greater sensitivity, such as lower pain threshold as compared to men [11,28]. Also, clinical pain are often reported differently with higher severity and frequency, longer duration, and present in a greater number of body regions in women as compared to men [6,34].

The mechanisms underlying these differences are still unclear [29,34]. The proposed influencing factors, such as biological [1,2,6,33] as well as psychological and psychosocial

factors [10], could all contribute to the different pain perceptions.

Varied responses to pharmacological pain-alleviation in women and men have been reported [4] and were demonstrated by Gear and collaborators [12–14] when opioids, mainly acting at the κ -receptor, were prescribed to patients with postoperative oral pain. Although non-pharmacological alternatives such as transcutaneous electrical nerve stimulation, TENS, are widely used for acute and chronic pain, the possibility of gender-related responses has to our knowledge yet not been investigated.

Hypoalgesia induced by TENS is based on endogenous pain inhibitory control and attributed to the inhibited propagation of pain-impulses in the dorsal horn at the spinal cord level following the electrical stimulation of myelinated af-

* Corresponding author. Tel.: +46 8 52487262; fax: +46 8 327026.

E-mail address: irene.lund@fyfa.ki.se (I. Lund).

ferent nerve fibres [17]. The induced effects are often documented as increased pain thresholds in healthy subjects and patients in pain [7,36] as well as inhibition of perception and processing of pain [32].

Documentation of gender differences in responses to TENS, by assessed sensory and pain thresholds does not to our knowledge exist. Therefore, the aim of this study was to evaluate the changes in electrocutaneous sensory and pain thresholds following TENS with high frequency, 80 Hz, in healthy women and men.

Healthy women and men, students of the physiotherapy program at the Karolinska Institutet were recruited to the study. The experiments were conducted in accordance with the declaration of Helsinki and the purpose of the trial was presented to the subjects who then gave their informed consent to participation. The study protocol was approved by the ethic committee of the Karolinska Hospital, dnr 01-169.

The main variables were sensory and pain thresholds, evaluated by means of electrocutaneous stimulation of one hand. The assessments of the two thresholds were observed four times at 10 min intervals—pre-, during- and posttranscutaneous electrical nerve stimulation, TENS—30 min in all.

For the threshold assessments, the subjects were instructed to press the electrodes of the electrical stimulation unit, with the thumb and second finger of one hand. The first perception of a pricking sensation was interpreted as the electrical sensory threshold, and the subjects were told to release the fingers. To assess the electrical pain threshold, the subjects were told to press the electrodes and not release the fingers until the pricking sensation altered to the first sensation of pain. The threshold values at the respective levels were automatically recorded immediately after the fingers were released from the electrodes, but were not divulged to the subjects until afterwards, making them blind to the ongoing assessments. The stimulation equipment was stated as safe in that, due to its construction, it would not cause tissue damage at any level. Prior to the trial, the subjects tried out the threshold assessments three to four times in order to familiarize themselves with the procedures.

The threshold assessment procedure (PainMatcher[®], Cefar Medical AB, Sweden) is based on non-invasive electrocutaneous stimulation of the skin of one hand, designed for clinical pain evaluation of assessing thresholds for sensory detection and pain. The procedure has earlier been shown reliable in test of reliability in healthy female volunteers and patients in pain [22]. The threshold assessment unit is microprocessor controlled and the generated current is distributed with a monophasic rectangular pulse of 15 mA and 10 Hz at random velocity. The output intensity increases by gradually widening the pulse duration in steps of 4 μ s to a maximum of 396 μ s, i.e. in a total of 99 steps. The assessed value, ranging from 1 to 99, relates directly to the output, where 1 corresponds to pulse duration of 4 μ s and 99 corresponds to 396 μ s. The maximum electrical charge per pulse is 5.9 μ C. The contact surface area, and hence the resulting current density, is ensured by a certain load of minimum finger pressure

against the electrodes. Loads between 0 and 13 k Ω will secure the output of 15 mA, while insufficient grip will not produce any output and loading exceeding 13 k Ω will not affect the intended functionality of the threshold assessments.

High frequency TENS, 80 Hz, was used (Cefar Primo stimulator, Cefar Medical AB, Lund, Sweden) with distributed current in asymmetrical biphasic pulses, 100% compensated, pulse duration of 180 μ s and available amplitude of 0–60 mA. Carbon electrodes, \sim 12 cm² coated with conducting gel, were fixed to the skin at the medial dorsal side of one forearm, i.e. the same side as for threshold assessments, and connected to the TENS unit. The negative electrode (cathode) was positioned 5 cm distal to the elbow joint and the positive electrode (anode) 5 cm proximal to the wrist joint, i.e. intra-segmental (dermatome C6–8) to the electrical threshold assessments. The current amplitude of the TENS was increased until a sensation just below unpleasantness was felt and without muscle contraction, representing approximately two to three times the perceived sensory detection level induced by TENS (\sim 7–15 mA). The subjects were instructed to maintain this level and to adjust the intensity level in case of adaptation, perceived as a decrease, during the TENS period. When assessing thresholds during stimulation, the current of the TENS unit was temporarily cut off.

The mean value and standard deviation (S.D.) were calculated for age and the threshold assessments were presented as the median and range (minimum to maximum) for the numerical units of the PainMatcher (PM) values. Evaluation of change in electrical sensory and pain thresholds, is based on pairs of ordinal individual data shown as PM values in square contingency tables for data ranging over few values as in assessed electrical sensory thresholds, and in scatter plots for data ranging over more values as in assessed electrical pain thresholds. The proportions of subjects with increased, unchanged, and decreased threshold values on the second occasion were calculated, as the 95% confidence intervals (95% CI) were, in proportions between the two independent groups.

The hypotheses of no change in assessed thresholds between pre-TENS and post-TENS were analyzed by the non-parametric sign test with correction for continuity [3]. In order to further evaluate and describe the change in terms of systematic change in common for the group and additional individual variations in change, not explained by the systematic change, a non-parametric rank-based method was used [30,31].

A systematic change appears as different marginal distributions of assessments in the contingency tables and plots. The measure of systematic change in position, relative position (RP), was calculated as the difference between the estimated probabilities of the first set of marginal distributions, being shifted towards decreased and towards increased values relative to the second set. Possible values of RP range from -1 to 1 . A positive RP value indicates increased thresholds on the second occasion and the contrary holds for the negative RP values.

A presence of systematic change was illustrated by plotting the two sets of cumulative proportions of the marginal distributions against each other. A non-zero RP value means that this so called ROC curve deviates from the diagonal. The more the ROC curve is deviated, the more systematic change in subjective assessments is present. A systematic change towards increased thresholds, positive RP, is evident by a ROC curve below the main diagonal.

A presence of individual variation in change, that could not entirely be explained by a systematic change, is evident from dispersed pairs of observations in the contingency tables of electrical sensory thresholds or in the scatter plots of electrical pain thresholds data. The relative rank variance (RV), expresses this individual variation, and ranges from 0 to 1. The higher the values of RV, the more dispersed the observations [31]. The evaluation of the systematic changes reflects the treatment efficacy on the entire group. Strong evidences of additional individual changes, high RV values, indicate that individually designed interventions would be preferable.

STATISTICA 6.0 was used to calculate descriptive statistics. The software package SYSRAN 1.0 for Matlab 6 was used to calculate the measures of RP and RV, and their corresponding 95% confidence intervals, CI. A p -value less than 0.05 was regarded as significant.

Twenty-nine women and 29 men ($n = 29$ per group) with mean ages of 27.7 years (S.D.: 6.8) and 27.8 years (S.D.: 6.9) participated in this study. Some of the participant's did not document all assessments.

The median levels (Range) given as PM values of the assessed electrical sensory thresholds pre-, during-, and post-TENS were for the women 3 (Range: 1–6), 4 (Range: 2–7), 4 (Range: 1–7) and 4 (Range: 1–8). The corresponding levels were for the men 4 (Range: 2–8), 5 (Range: 2–8), 5 (Range: 2–9) and 6 (Range: 3–9) (Fig. 1).

For the whole group, the electrical sensory threshold values post-TENS increased compared to the pre-TENS values in 36 of the 52 (69%) documented responses, 9 of the 52 (17%) were unchanged, and 7 of the 52 (13%) were decreased, $p < 0.001$. When evaluating these post-TENS effects, separated into women and men, the electrical sensory thresholds was increased in 15 of the 25 responding women (60%), unchanged in 5 of 25 (20%), and decreased in 5 of 25 (20%). At the same point of time the same threshold was increased in 21 of the 27 men (78%), unchanged in 4 of 27 (15%), and decreased in 2 of 27 (7%) (Fig. 2a and b). The difference between proportions in women and men with increased electrical sensory thresholds values was -18% (95% CI, -43% , 7%).

The further evaluation of this systematic change was confirmed by the measured RP indicating a shift to increased electrical sensory thresholds for both women and men (RP, 0.35; 95% CI, 0.07, 0.63; and RP, 0.36; 95% CI, 0.17, 0.54, respectively). This is also demonstrated by the two deviating ROC-curves (Fig. 2c). In the women, a significant additional individual variability, measured by the RV, was observed (RV, 0.61; 95% CI, 0.17, 1.00) while this measure was considered

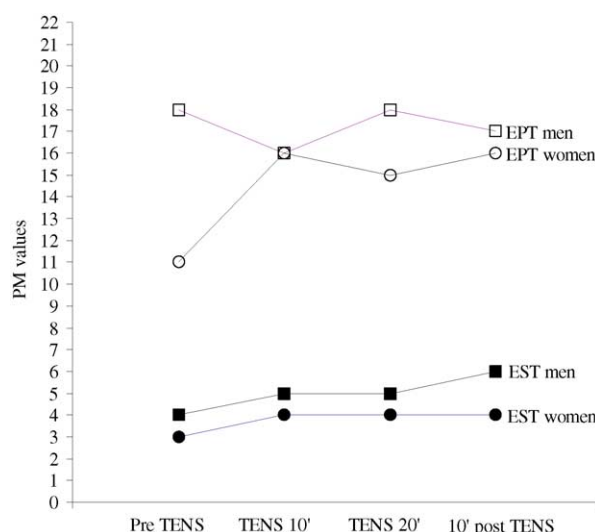


Fig. 1. Median PainMatcher values of assessed electrical sensory threshold, EST, and electrical pain threshold, EPT, in response to transcutaneous electrical nerve stimulation, TENS, with high frequency. Assessments were observed before (pre-) TENS, EST women $n = 29$ and men $n = 28$, EPT women $n = 29$ and men $n = 29$; during-TENS (TENS 10 min), EST women $n = 29$ and men $n = 29$, EPT women $n = 29$ and men $n = 29$; immediately after TENS (TENS 20 min), EST women $n = 29$ and men $n = 27$, EPT women $n = 29$ and men $n = 28$; 10 min after (post) TENS, EST women $n = 25$ and men $n = 27$, EPT women $n = 27$ and men $n = 27$.

small and negligible in men (RV, 0.05; 95% CI, 0.00, 0.11). According to the RV values, the variation is related to the women and not to the men.

The median level of the assessed electrical pain thresholds for the women were at the different time points 11 (Range: 6–21), 16 (Range: 5–29), 15 (Range: 6–27) and 16 (Range: 6–30). For the men, the corresponding values were 18 (Range: 8–57), 16 (Range: 7–63), 18 (Range: 9–48) and 17 (Range: 8–51) (Fig. 1). Post-TENS, the pain threshold was significantly changed and had increased in 37 of the 54 (68%) responding subjects, was unchanged in 5 of 54 (9%) and had decreased in 12 of 54 (22%), $p < 0.001$. By separating the results into women and men, it was shown that the pain threshold had increased in 23 of the 27 women (85%), was unchanged in 3 of 27 (11%) and had decreased in 1 of 27 (4%), $p < 0.001$. Among the men, the pain threshold was not significantly changed but had increased in 14 of 27 (52%), was unchanged in 2 of 27 (7%), and had decreased in 11 of 27 individuals (41%), $p = 0.69$ (Fig. 3a and b). A significantly greater proportion of women than men increased their pain threshold values post-TENS, 33% (95% CI, 11%, 57%). This difference in systematic change between women and men was confirmed by the RP values, where the RP in women significantly differed from zero (RP, 0.43; 95% CI, 0.27, 0.60; and RP, -0.01 ; 95% CI, -0.13 , 0.10, respectively). The corresponding ROC-curves illustrate this gender difference in systematic changes in which the curve for the men is close to the main diagonal (Fig. 3c).

The women's electrical pain threshold responses showed an additional significant individual variation (RV, 0.20; 95%

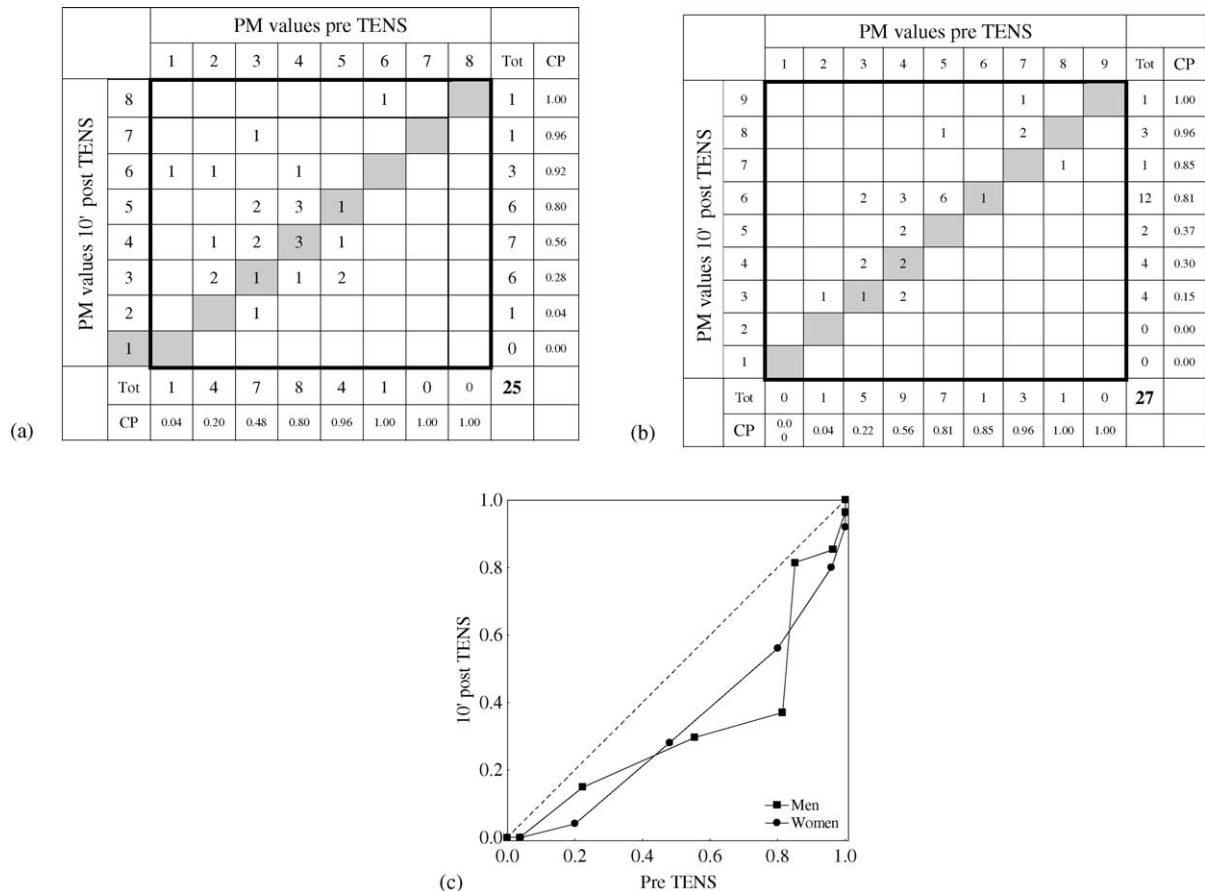


Fig. 2. (a–c) Observed paired assessments in PM values of electrical sensory threshold (EST) before (pre-) compared to 10 min post-TENS. Joint distribution of EST shown in contingency tables among women, $n=25$ (a), and men, $n=27$ (b). Tot: total; CP: cumulative proportion. Relative operative characteristic curve, ROC curve, (c) shows the cumulative proportions of EST in women and men, respectively.

CI, 0.01, 0.39), while the men's individual variation was considered as small (RV, 0.09; 95% CI, 0.00, 0.22).

The responses to high frequency TENS in this study showed a rapid onset of systematical changes towards increased electrical sensory thresholds in both women and men that were present during the whole observation period. Interestingly, only the women demonstrated a similar systematical change of their electrical pain thresholds; the men's remained unchanged. Besides the women's responses of systematical change, their responses also showed a greater individual variability compared to the men. This sign of heterogeneity in women could be explained by a spread of their increased individual responses ranging from 1 to 5 PM values in assessed electrical sensory thresholds, and 1 to 13 PM values in assessed electrical pain thresholds, with the majority of responses exceeding an increase of 1 PM in both thresholds. For the men, the assessed increase of electrical sensory threshold varied from 1 to 3 PM values with the greater part not exceeding 1 PM value. Furthermore, this variability indicates that pain-alleviating treatment with TENS would be preferred to be individually designed.

Another observation was higher sensory and pain threshold in men compared to women at baseline. This gender difference in pain threshold assessments has been demonstrated earlier, but was shown to be depending on the type of noxious stimulus used [21,28].

Although women and men started from different thresholds before TENS, the high frequency TENS induced increase of sensory threshold intra-segmentally related to the electrical threshold assessments, which could be explained in both genders by an adaptive adjustment of the peripheral tissue and/or the activity in the afferent neurons.

The observed increase in pain thresholds present for the women in this study, is in line with previous reports [19,23,24,27,35] and is generally attributed to the TENS-induced activation of endogenous pain inhibitory systems, generally by local spinal mechanisms, according to the gate control theory. Endogenous opioids, such as dynorphins, enkephalins and β -endorphins working mainly at the κ -, δ -, and μ -receptors, respectively, are among the mediators suggested to play a key role in the seen hypoalgesia. Han et al. [16] reported that patients treated with high frequency TENS

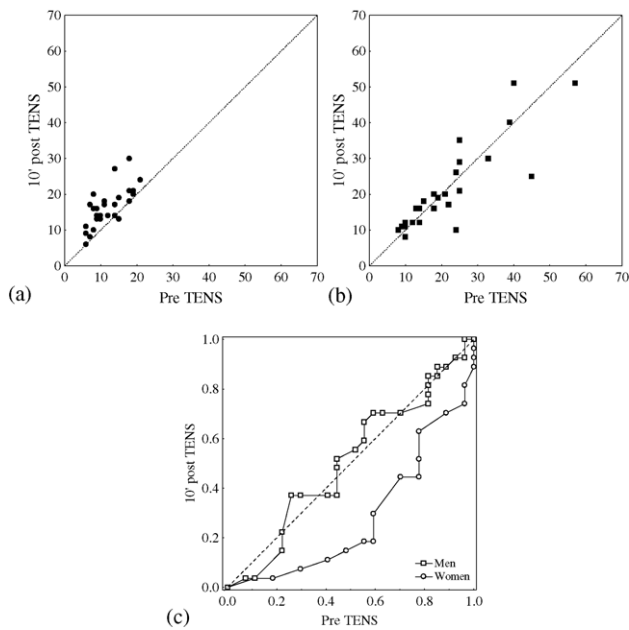


Fig. 3. (a–c) Observed paired assessments in PM values of electric pain threshold (EPT) before (pre-) compared to 10 min post-TENS. Joint distribution of EPT shown in scatter-plots among women, $n = 25$ (a), and men, $n = 27$ (b). Relative operative characteristic curve, ROC curve (c) shows the cumulative proportions of EPT in women and men, respectively.

for 30 min applied to the hand and leg results in an increase of dynorphin A in the cerebrospinal fluid. The possible release of dynorphin as a response to electrical stimulation at high frequency may explain the increased pain thresholds in women. This suggestion is supported by Gear and collaborators who have reported that female patients with postoperative oral pain perceived less pain than male patients in response to κ -opioid agonists. The mechanisms of the seen gender differences of the assessed electrical pain thresholds are not known, but probably due to complex interdependent biological, psychological and psychosocial mechanisms. An interaction of gonadal hormones with opioid systems may provide a partial explanation for the reported differences supported by results from human [5,25,38] as well as animal studies [8,9]. Possibly different gender role expectancies [37] as well as differences in changed attention could also reflect the changes in gender-related determined pain thresholds.

A limitation of this study may be the lack of control for menstrual phase effects. Electrical pain threshold assessments in relation to the menstrual cycle have been reported as increased during the luteal phase [15] or as unchanged during both the follicular and luteal phase of the menstrual cycle [26]. The latter method, using electrocutaneous stimulation to one index finger, has similarities with the technique used by us. It is likely that the effects obtained on pain thresholds by high frequency TENS may not be explained by the phases of the menstrual cycle.

To further explore the TENS-induced effects, an additional group of no stimulation could have been included into the study. Earlier observations of repeated assessments with this

technique without any sensory stimulation, however, showed no systematic variability in the assessment of the pain threshold (Lund et al., 2004). It is, therefore, unlikely that the effects seen following TENS can be attributed to learning effects. If there would have been a learning effect, one would expect the thresholds to decrease as part of a learning experience, and this was not the case. Hence, a group without any stimulation was not included.

The assessment of electrocutaneous thresholds in healthy subjects may be an effective tool in experimental pain research as it detects the stature of endogenous pain inhibitory systems. In clinical practice, pain threshold assessments could be used to monitor changes in pain over time [18,20]. Using this procedure, pain thresholds may be assessed both within as well as outside the area of pain (unpublished observations).

The present results show that the subjects in this study responded to high frequency TENS in a gender-related manner at the electrical pain threshold level. Women's thresholds were systematically increased whereas the men's were unaffected on the group level. On an individual basis some men reported an increase in thresholds. However, others did not, and some even reported a decrease. To our knowledge, other studies on TENS-induced effects on pain thresholds have not reported on gender-related differences. Taken together, a plausible interpretation is that women may benefit from high frequency TENS whereas the response from men varies. This assumption is presently under investigation.

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References

- [1] M. al-Absi, K.L. Petersen, L.E. Wittmers, Adrenocortical and hemodynamic predictors of pain perception in men and women, *Pain* 96 (2002) 197–204.
- [2] A.M. Aloisi, Gonadal hormones and sex differences in pain reactivity, *Clin. J. Pain* 19 (2003) 168–174.
- [3] D. Altman, *Practical Statistics for Medical Research*, Chapman and Hall, London, 1991, pp. 186–189.
- [4] M. Anthony, M.J. Berg, Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part I. Workshop held at the National Institutes of Health, May 4–6, 1999, *J. Womens Health Gender Based Med.* 11 (2002) 601–615.
- [5] R.E. Bartok, R.M. Craft, Sex differences in opioid antinociception, *J. Pharmacol. Exp. Ther.* 282 (1997) 769–778.
- [6] K.J. Berkley, Sex differences in pain, *Behav. Brain Sci.* 20 (1997) 371–380.
- [7] L. Chesterton, P. Barlas, N. Foster, T. Lundeberg, C. Wright, G. Baxter, Sensory stimulation (TENS): effects of parameter manipulation on mechanical pain thresholds in healthy human subjects, *Pain* 99 (2002) 253–262.
- [8] T.J. Cicero, B. Nock, E.R. Meyer, Sex-related differences in morphine's antinociceptive activity: relationship to serum and brain mor-

- phine concentrations, *J. Pharmacol. Exp. Ther.* 282 (1997) 939–944.
- [9] C.D. Cook, A.C. Barrett, E.L. Roach, J.R. Bowman, M.J. Picer, Sex-related differences in the antinociceptive effects of opioids: importance of rat genotype, nociceptive stimulus intensity and efficacy at the my opioid receptor, *Psychopharmacology* 150 (2000) 430–442.
- [10] R.B. Fillingim, Sex, gender and pain a biopsychosocial framework, in: R.B. Fillingim (Ed.), *Sex, Gender and Pain. Progress in Pain Research and Management*, vol. 17, IASP Press, Seattle, 2000, pp. 1–6.
- [11] R.B. Fillingim, W. Maixner, Gender differences in the responses to noxious stimuli, *Pain Forum* 4 (1995) 209–221.
- [12] R.W. Gear, N.C. Gordon, P.H. Heller, S.M. Paul, C. Miakowski, J.D. Levine, Gender difference in analgesic response to the kappa-opioid pentazocine, *Neurosci. Lett.* 205 (1996) 207–209.
- [13] R.W. Gear, C. Miaskowski, N.C. Gordon, S.M. Paul, P.H. Heller, J.D. Levine, Kappa-opioids produce significantly greater analgesia in women than in men, *Nat. Med.* 11 (1996) 1248–1250.
- [14] R.W. Gear, C. Miaskowski, N.C. Gordon, S.M. Paul, P.H. Heller, J.D. Levine, The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain, *Pain* 83 (1999) 339–345.
- [15] M.A. Giamberardino, K.J. Berkley, S. Iezzi, P. de Bigontina, L. Vecchiet, Pain threshold variations in somatic wall tissues as a function of menstrual cycle, segmental site and tissue depth in non-dysmenorrheic women, dysmenorrheic women and men, *Pain* 71 (1997) 187–197.
- [16] J.S. Han, X.H. Chen, S.L. Sun, X.J. Xu, Y. Yuan, S.C. Yan, J.X. Hao, L. Terenius, Effect of low- and high-frequency TENS on Met-enkephalin-Arg-Phe and dynorphine A immunoreactivity in human lumbar CSF, *Pain* 47 (1991) 295–298.
- [17] P. Hansson, T. Lundeberg, Transcutaneous electrical nerve stimulation, vibration and acupuncture as pain relieving measurers, in: P.D. Wall, R. Melzack (Eds.), *Textbook of Pain*, fourth ed., Churchill Livingstone, London, 1999, pp. 951–965.
- [18] D. He, K.B. Veiersted, A.T. Hostmark, J.I. Medbo, Effect of acupuncture treatment on chronic neck and shoulder pain in sedentary female workers: a 6-month and 3-year follow-up study, *Pain* 109 (2004) 299–307.
- [19] M.I. Johnson, V.K. Hajela, C.H. Ashton, J.W. Thompson, The effects of auricular transcutaneous electrical nerve stimulation (TENS) on experimental pain threshold and autonomic function in healthy subjects, *Pain* 46 (1991) 337–342.
- [20] M. Karst, J.D. Rollnik, M. Fink, M. Reinhard, S. Piepenbrock, Pressure pain threshold and needle acupuncture in chronic tension-type headache—a double-blind placebo-controlled study, *Pain* 88 (2000) 199–203.
- [21] S. Lautenbacher, G.B. Rollman, Sex differences in responsiveness to painful and non-painful stimuli are dependent upon the stimulation method, *Pain* 53 (1993) 255–264.
- [22] I. Lund, T. Lundeberg, J. Kowalski, C. Budh, L. Sandberg, E. Svensson. Evaluation of variations in sensory and pain threshold assessments by electrocutaneous stimulation. *Physiother. Theor. Pract.*, in press.
- [23] S. Marchand, M.C. Bushnell, G.H. Duncan, Modulation of heat pain perception by high frequency transcutaneous electrical nerve stimulation (TENS), *Clin. J. Pain* 7 (1991) 122–129.
- [24] B.C. McDowell, K. McCormack, D.M. Walsh, D.G. Baxter, J.M. Allen, Comparative analgesic effects of H-wave therapy and transcutaneous electrical nerve stimulation on pain threshold in humans, *Arch. Phys. Med. Rehab.* 80 (1999) 1001–1004.
- [25] S.S. Negus, N.K. Mello, Opioid antinociception in ovariectomized monkeys: comparison with antinociception in males and effects of estradiol replacement, *J. Pharmacol. Exp. Ther.* 290 (1999) 1132–1140.
- [26] M. Oshima, R. Ogawa, D. Londyn, Current perception threshold increases during pregnancy but does not change across menstrual cycle, *J. Nippon Med. Sch.* 69 (2002) 19–23.
- [27] L. Rieb, B. Pomeranz, Alterations in electrical pain thresholds by use of acupuncture-like transcutaneous electrical nerve stimulation in pain-free subjects, *Phys. Ther.* 72 (1992) 658–667.
- [28] J.L. Riley III, M.E. Robinson, E.A. Wise, C.D. Myers, R.B. Fillingim, Sex differences in the perception of noxious experimental stimuli: a meta-analysis, *Pain* 74 (1998) 181–187.
- [29] G.B. Rollman, S. Lautenbacher, K.S. Jones, Sex and gender differences in responses to experimentally induced pain in humans, in: R.B. Fillingim (Ed.), *Sex, Gender and Pain. Progress in Pain Research and Management*, vol. 17, IASP Press, Seattle, 2000, pp. 165–190.
- [30] E. Svensson, Application of rank-invariant method to evaluate reliability of ordered categorical assessment, *J. Epid. Biostat.* 4 (1998) 403–409.
- [31] E. Svensson, J.E. Starmark, Evaluation of individual and group changes in social outcome after aneurismal subarachnoid haemorrhage: a long-term follow-up study, *J. Rehab. Med.* 34 (2002) 251–259.
- [32] M. de Tommaso, P. Fiore, A. Camporeale, M. Guido, G. Libro, L. Losito, M. Megna, F. Puca, G. Megna, High and low frequency transcutaneous electrical nerve stimulation inhibits nociceptive responses induced by CO₂ laser stimulation in humans, *Neurosci. Lett.* 342 (2003) 17–20.
- [33] M. Torgén, C. Swerup, Individual factors and physical work in relation to sensory thresholds in a middle-aged general population sample, *Eur. J. Appl. Physiol.* 86 (2002) 418–427.
- [34] Unruh, Review article—gender variations in clinical pain experience, *Pain* 65 (1996) 123–167.
- [35] D.M. Walsh, A.S. Lowe, K. McCormack, J.C. Willer, G.D. Baxter, J.M. Allen, Transcutaneous electrical nerve stimulation: effect on peripheral nerve conduction, mechanical pain threshold, and tactile threshold in humans, *Arch. Phys. Med. Rehab.* 79 (1998) 1051–1058.
- [36] E.G. Widerstrom, P.G. Aslund, L.E. Gustafsson, C. Mannheimer, S.G. Carlsson, S.A. Andersson, Relations between experimentally induced tooth pain threshold changes, psychometrics and clinical pain relief following TENS. A retrospective study in patients with long-lasting pain, *Pain* 51 (1992) 281–287.
- [37] E.A. Wise, D.D. Price, C.D. Meyers, M.W. Heft, M.E. Robinson, Gender role expectations of pain: relationship to experimental pain perception, *Pain* 96 (2002) 335–342.
- [38] J.K. Zubieta, Y.R. Smith, J.A. Bueller, Y. Xu, M.R. Kilbourn, D.M. Jewett, C.R. Meyer, R.A. Koeppe, C.S. Stohler, μ -Opioid receptor-mediated antinociceptive responses differ in men and women, *J. Neurosci.* 22 (2002) 5100–5207.