No evidence of widespread mechanical pressure hyperalgesia after experimentally induced central sensitization through skin nociceptors

Timothée Cayrol[a], Laurent Pitance[a], Nathalie Roussel[b], André Mouraux[c], Emanuel N. van den Broeke[c,*]

Abstract

Introduction: An increasing number of clinical studies involving a range of chronic pain conditions report widespread mechanical pressure pain hypersensitivity, which is commonly interpreted as resulting from central sensitization (CS). Secondary hyperalgesia (increased pinprick sensitivity surrounding the site of injury) is considered to be a manifestation of CS. However, it has not been rigorously tested whether CS induced by peripheral nociceptive input involves widespread mechanical pressure pain hypersensitivity.

Objectives: The aim of this study was to assess whether high-frequency electrical stimulation (HFS), which induces a robust secondary hyperalgesia, also induces a widespread decrease of pressure pain thresholds (PPTs).

Methods: We measured PPTs bilaterally on the temples (temporalis muscles), on the legs (tibialis anterior muscles), and on the ventral forearm (flexor carpi radialis muscles) before, 20 minutes after, and 45 minutes after applying HFS on the ventral forearm of sixteen healthy young volunteers. To evaluate the presence of secondary hyperalgesia, mechanical pinprick sensitivity was assessed on the skin surrounding the site where HFS was applied and also on the contralateral arm.

Results: HFS induced a significant increase in mechanical pinprick sensitivity on the HFS-treated arm. However, HFS did not decrease PPTs neither in the area of increased pinprick sensitivity nor at more distant sites.

Conclusion: This study provides no evidence for the hypothesis that CS, induced after intense activation of skin nociceptors, involves a widespread decrease of PPTs.

Keywords: High-frequency electrical stimulation, Central sensitization, Secondary hyperalgesia, Pressure pain thresholds

1. Introduction

An increasing number of clinical studies involving a wide range of chronic pain conditions such as chronic low back pain, temporomandibular joint disorders, and osteoarthritis report widespread mechanical pain hypersensitivity, demonstrated by reduced pressure pain thresholds (PPTs) at several body

regions.[2,14] This widespread hypersensitivity is commonly interpreted as resulting from central sensitization (CS).[2,30,41]

The taskforce for taxonomy of the International Association for the Study of Pain (IASP) defines CS as: "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input."[24] In a related note, the taskforce also mentions that sensitization refers to "*a neurophysiological term that can only be applied when both input and output of the neural system under study is known, eg, by controlling the stimulus and measuring the neural event*."

According to Treede,[33] secondary hyperalgesia[15] induced by intradermal capsaicin injection is currently the only example where input and output of the system is known and the definition of CS is fulfilled. Capsaicin activates nociceptors expressing the TRPV-1 receptor. As a result, a large area of the skin surrounding the capsaicin site becomes more sensitive to mechanical pinprick stimuli (ie, secondary mechanical pinprick hyperalgesia). A previous study using intradermal capsaicin injection in primates showed that pinprick stimuli delivered to the skin surrounding the injection site elicited increased responses of both wide dynamic range and high-threshold spinal nociceptive neurons.[29] In another study, performed by the same group, no evidence was found for a peripheral sensitization of both mechano- and heat-sensitive A-fiber nociceptors type I (AMH-I) and mechano- and

heat-sensitive C-fiber nociceptors (CMH) after intradermal capsaicin injection,[4] suggesting that secondary pinprick hyperalgesia in humans mainly results from an increased responsiveness of spinal nociceptive neurons (CS).

Secondary pinprick hyperalgesia can also be induced after high-frequency electrical stimulation of skin nociceptors.[8,9,16,19] Indeed, HFS induces a pronounced increase in mechanical pinprick sensitivity in a large area of the skin beyond the area at which HFS was applied.

The attribution of widespread reduced PPTs to CS, while frequently asserted in clinical research, has not been rigorously tested experimentally. Therefore, the aim of this study was to use HFS to induce secondary hyperalgesia and to assess whether it leads to widespread mechanical pressure hyperalgesia.

2. Methods

2.1. Participants

Sixteen healthy students were included in this experiment (9 females, 7 males; aged 21–23 years; 22.1 ± 1.1 years [mean ± SD]). Exclusion criteria were: (1) experiencing a preexisting pain condition; (2) self-reported medication (except contraceptives) consumption and/or self-reported recreational drug use; (3) presenting any medical conditions, including neurological and psychiatric diseases; (4) participation to more than 6 hours per week of sport; and (5) exhibiting sign of damage at or near the ventral forearm.

The experiment was conducted according to the Declaration of Helsinki, and approval for the experiment was obtained from the local ethical committee. All participants signed an informed consent form and received financial compensation for their participation. Participants were naive regarding the hypothesis of the study.

2.2. Design

During the experiment, participants were comfortably seated in a chair with their arms resting on a table in front of them with palms up. Pressure pain thresholds were evaluated 3 times: before HFS (T0), 20 minutes after HFS (T1), and 45 minutes after HFS (T2). Pressure pain thresholds were measured bilaterally: (1) on the anterior portions of the temporalis muscle, 1 cm posterior to the bony crest lateral to the eyebrow and 1 cm superior to the zygomatic process of the temporal bone,[1] (2) on the tibialis anterior muscle, approximately 2.5 cm lateral and 5 cm inferior to the tibial tubercle,[39] and (3) on the flexor carpi radialis muscle, inside the "test area" (**Fig. 1A**). The time points T1 and T2 were chosen because previous studies have shown that pinprick hyperalgesia induced by HFS is maximal between 20 and 30 minutes after HFS.[27]

2.3. Transcutaneous high-frequency electrical stimulation

HFS was applied on the left or right volar forearm (10 cm distal to the cubital fossa) as previously described.[8,9,19] In summary, HFS consisted of 5 trains of 100-Hz electrical pulses (pulse width: 2 ms) lasting 1 second each. The time interval between each train was 10 seconds. The intensity of stimulation was individually adjusted to 20× the absolute detection threshold to a single pulse (0.23 ± 0.10 mA; mean ± SD). The electrical pulses were triggered by a programmable pulse generator (Master-8; AMPI, Jerusalem, Israel) and produced by a constant current electrical stimulator (Digitimer DS7A; Digitimer, Welwyn Garden City, United Kingdom).

Electrical pulses were delivered to the skin using a specifically designed electrode designed and built at the Centre for Sensory-Motor Interaction (Aalborg University, Denmark). The cathode consists of 16 blunt stainless-steel pins with a diameter of 0.2 mm protruding 1 mm from the base. The 16 pins are placed in a circle with a diameter of 10 mm. The anode consists of a surrounding stainless-steel ring having an inner diameter of 22 mm and an outer diameter of 40 mm (**Fig. 1**).

To avoid any confounding effect of handedness, the arm onto which HFS was applied (dominant vs nondominant) was counterbalanced across participants. Handedness was assessed using the Flinders Handedness Survey.[25]

2.4. Mechanical pinprick stimulation

To assess the presence secondary mechanical hyperalgesia after HFS, we delivered mechanical pinprick stimuli before (T0) and approximately 55 minutes after HFS (T2) in the area surrounding the HFS stimulation ("test area") and on the homologous site of the contralateral control arm with a calibrated 128-mN pinprick probe (The PinPrick; MRC Systems GmbH, Heidelberg, Germany). A total of 3 mechanical stimuli were delivered; then, participants were asked to report the average intensity of perception elicited by the 3 pinprick stimuli on a numerical rating scale ranging from 0 (no perception) to 100 (maximal pain), with 50 representing the transition from nonpainful to painful domains of sensation. We used this scale because in previous studies, pinprick stimuli delivered with a force of 128 mN were on average not perceived as painful at baseline, but in some cases became painful after HFS.[8,23,31,32] The present scale allows for the quantification of sensations changing from being nonpainful to being painful. To avoid sensitization of the stimulated skin, the pinprick stimulus was not applied twice on the same location.

To prevent the experience of increased pinprick sensitivity to bias the participants during the PPT measurements, we only assessed pinprick sensitivity at the beginning and the end of the experiment.

2.5. Pressure pain thresholds

Pressure pain thresholds were assessed by applying increased pressure delivered with a pressure gauge device with a probe area of 1 cm² (FDX50; Wagner Instruments, Greenwich, CT) to the skin. Participants were instructed to say "stop" as soon as the pressure started to become painful. At each measurement, PPTs were assessed 3 times, with a 30-second interstimulus interval,[5] and the arithmetic mean of the 3 repeated measures was used for analysis.[20] At the beginning of the experiment, the areas at which the PPTs were measured were marked to allow for consistency of the tested area, and participants were familiarized to the assessment of their PPTs.

2.6. Statistical analyses

Statistical analyses were conducted using SPSS 25 (SPSS, Chicago, IL). To confirm the successful induction of increased pinprick sensitivity after HFS, we performed a General Linear Model repeated-measures analysis of variance (ANOVA) analysis using 2 within-subject factors: time (pre vs post) and arm (control vs HFS arm) on the dependent-variable numerical rating scale score. To assess changes in PPTs after HFS, we performed a repeated-measures ANOVA analysis using 2 within-subject factors: time (3 levels: T0, T1 and T2) and arm (with 2 levels: control vs HFS arm) on the PPTs measured at (1) the skin
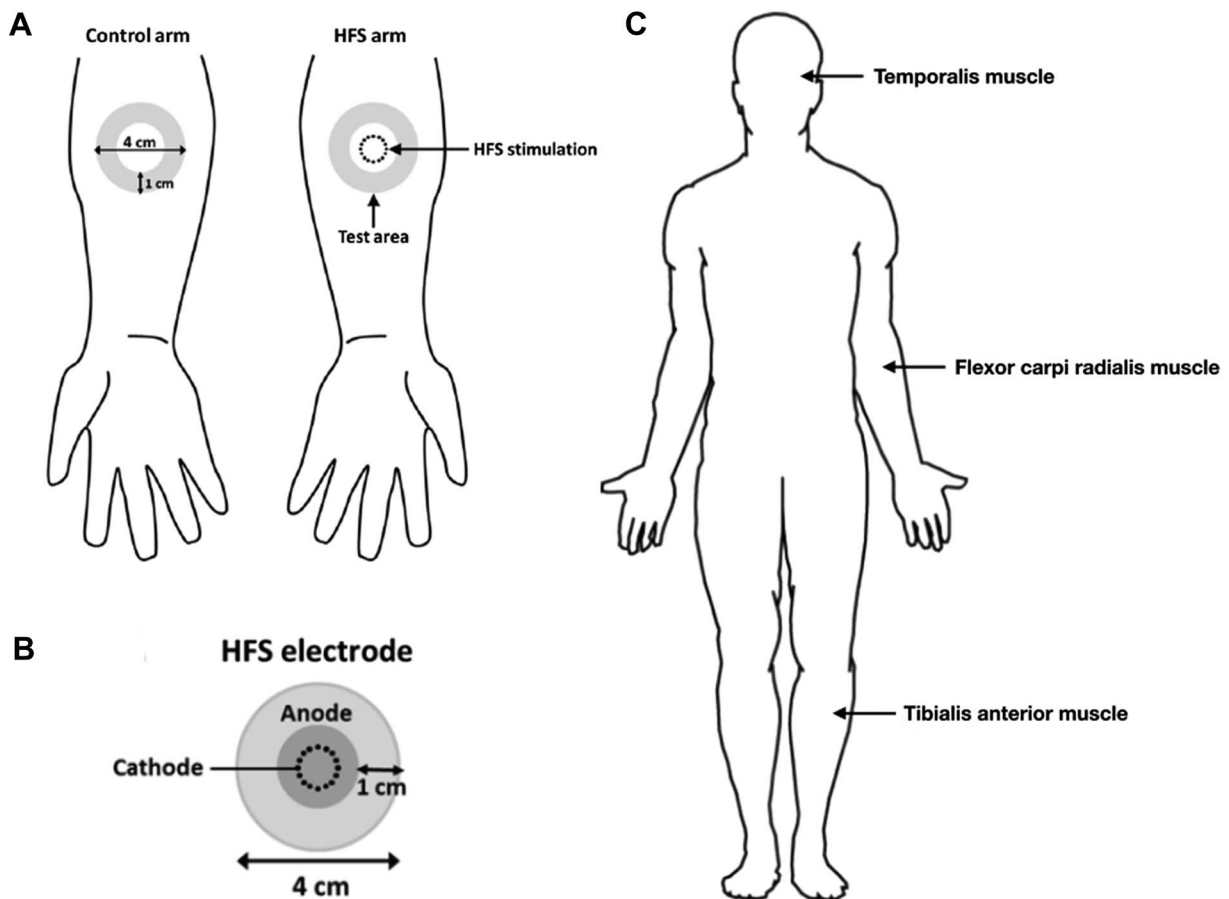
Figure 1. Experimental setup. (A) High-frequency electrical stimulation (HFS) was applied to the ventral forearm of one arm. Pinprick stimuli were applied to the skin surrounding the site at which HFS was applied and to the homologous area of the contralateral arm that served as control. (B) The electrode used to deliver HFS consisted of 16 blunt stainless-steel pins placed in a 10-mm diameter ring (cathode), surrounded by a concentrically located anode having an inner diameter of 22 mm and an outer diameter of 40 mm. (C) Pressure pain thresholds were assessed bilaterally on the anterior portions of the temporalis muscle, on the tibialis anterior muscle, and on the flexor carpi radialis muscle (in the "test" area).

surrounding the site at which HFS was applied (and to the homologous area of the contralateral arm); (2) the temples; and (3) the legs.

The assumption of sphericity was tested using Mauchly test. In case the data violated the assumption of sphericity, F-values were corrected using the Greenhouse–Geisser procedure (denoted F_{G-G}). The level of significance was set at $P < 0.05$.

3. Results

3.1. Mechanical pinprick sensitivity

HFS induced a clear increase in pinprick sensitivity at the HFS arm (**Fig. 2A**). This was confirmed by the repeated-measures ANOVA, which showed a significant time $\times$ treatment interaction ($F_{(1, 15)} = 35.493$, $P < 0.001$, partial $\eta^2 = 0.703$). Post hoc tests showed a statistically significant increase of the perceived intensity at the HFS-treated arm after HFS (paired t test; t (15) $= -5.729$, $P < 0.001$). No significant changes in perceived intensity were observed at the control arm ($P = 0.494$).

3.2. Pressure pain thresholds at the area of increased pinprick sensitivity

The repeated-measures ANOVA analysis of the PPTs measured at the area of increased pinprick sensitivity and contralateral control site did not show a significant main effect of time ($F_{(2, 30)} = 0.493$, $P =$

0.616, partial $\eta^2 = 0.032$), or main effect of arm ($F_{(1, 15)} = 0.481$, $P = 0.499$, partial $\eta^2 = 0.031$), or significant time $\times$ treatment interaction ($F_{(2, 30)} = 0.493$, $P = 0.616$, partial $\eta^2 = 0.032$; **Fig. 2B**).

3.3. Pressure pain thresholds at distant sites

The repeated-measures ANOVA of the PPTs measured on the anterior portion of the temporalis muscle did not show a significant main effect of time ($F_{(2, 30)} = 0.708$, $P = 0.501$, partial $\eta^2 = 0.045$), or a significant main effect of arm ($F_{(1, 15)} = 1.326$, $P = 0.268$, partial $\eta^2 = 0.081$), or a significant time $\times$ treatment interaction ($F_{(2, 30)} = 1.417$, $P = 0.258$, partial $\eta^2 = 0.086$; **Fig. 2C**).

The repeated-measures ANOVA of the PPTs measured on the tibialis anterior muscle did not show a significant main effect of time ($F_{(2, 30)} = 2.340$, $P = 0.114$, partial $\eta^2 = 0.135$), or main effect of arm ($F_{(1, 15)} = 0.334$, $P = 0.572$, partial $\eta^2 = 0.022$), or significant time $\times$ treatment interaction ($F_{(2, 30)} = 0.085$, $P = 0.919$, partial $\eta^2 = 0.006$; **Fig. 2D**).

3.4. Additional analysis

To strengthen our analysis regarding PPTs delivered in the area of secondary hyperalgesia, we post-hoc quantified the probability that the H0 hypothesis (ie, that HFS does not induce a significant decrease in PPT in the area of secondary hyperalgesia) is true as compared to the alternative H1 hypothesis (that HFS does induce
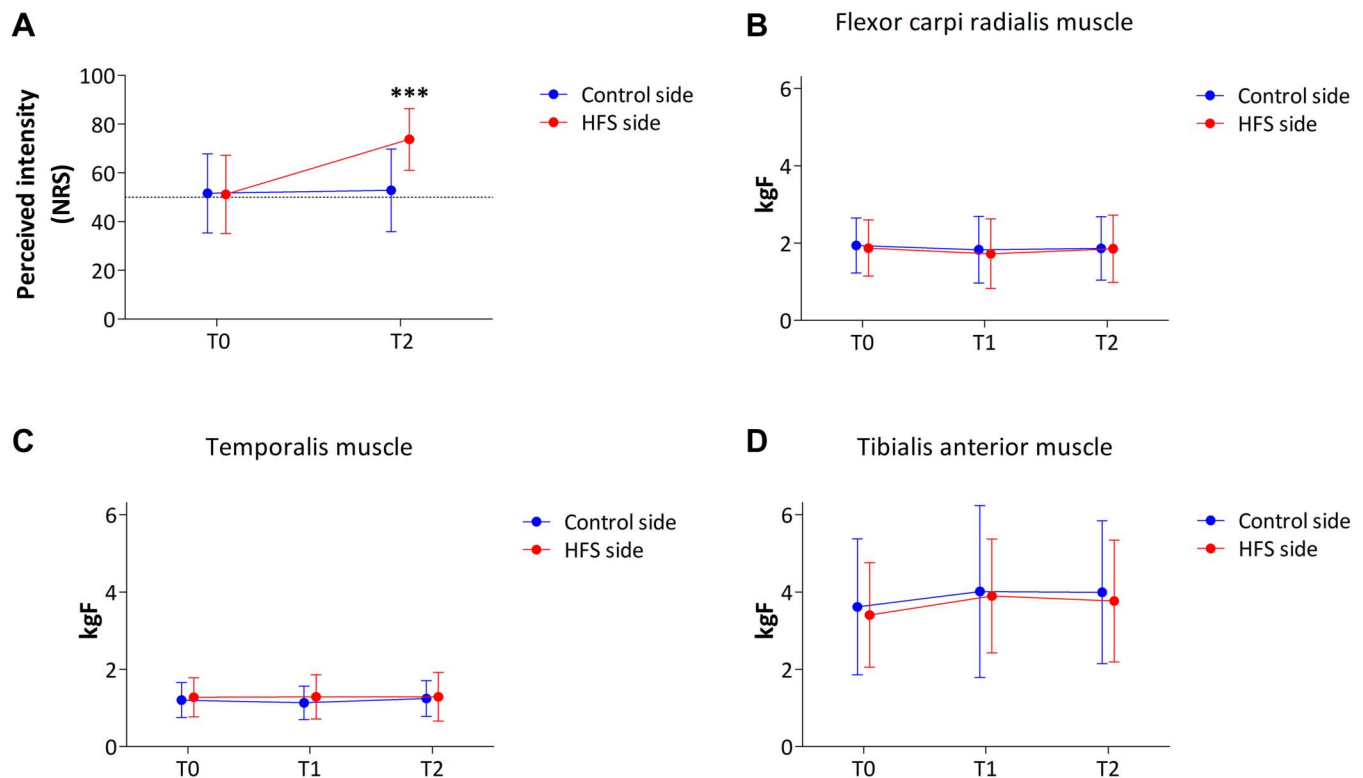
Figure 2. (A) Group-level average (and SD) intensity of perception elicited by the pinprick stimulation before (T0) and approximately 55 minutes after HFS (T2) in the area surrounding the HFS stimulation ("test area") and on the homologous site of the contralateral control arm. (B–D) Group-level average (and SD) pressure pain thresholds (PPTs) measured bilaterally from (B) the flexor radialis muscle (inside the "test area"), (C) the anterior portion of the temporalis muscle, and (D) the tibialis anterior muscle before (T0), approximately 20 minutes after HFS (T1), and approximately 45 minutes after HFS (T2). ***$P<.001$.

a decrease in PPT) by performing a Bayesian repeated-measures ANOVA.[32,38] The Bayesian analysis was performed in JASP. A 3 × 2 Bayesian repeated-measures ANOVA was performed on the PPTs measured from both arms using the within-subject factors: time (T0, T1, and T2) and side (control and HFS).

The Bayesian repeated-measures ANOVA provided moderate evidence in support of the H0 hypothesis that there is no main effect of time: BF10 = 0.229 (H1) vs BF01 = 4.735 (H0), suggesting that PPTs did not decrease after HFS. Furthermore, the Bayesian repeated-measures ANOVA provided strong evidence in support of the H0 hypothesis that there is no time × arm interaction: BF10 = 0.070 (H1) vs BF01 = 14.246 (H0), suggesting that there is no decrease in PPT after HFS in the area of secondary hyperalgesia, compared with control site.

4. Discussion

Our study provides no evidence that experimentally induced CS using high-frequency electrical stimulation of skin nociceptors induces a widespread mechanical pressure pain hyperalgesia. HFS induced a clear increase in mechanical pinprick hyperalgesia in the area surrounding the site at which HFS was applied (ie, area of secondary hyperalgesia). However, HFS did not induce a decrease in PPTs either in the area of secondary hyperalgesia or at more distant body sites.

4.1. No decrease in pressure pain thresholds in the area of secondary hyperalgesia

Despite the pronounced increase in mechanical pinprick sensitivity, we did not observe a decrease in PPTs after HFS in

the area of secondary hyperalgesia. Our results seem to be in contrast to the results of Klein et al.,[20] who did observe a small (8%) but significant decrease in PPTs in the area of secondary hyperalgesia induced by HFS. Vo and Drummond[34] also observed a significant decrease in PPTs after HFS in the area of secondary hyperalgesia. However, the same authors did not replicate this finding in 2 other studies.[35,36] Importantly, in the studies in which PPTs are significantly decreased,[20,34] the effect was small and lower than the commonly reported minimal detectable change for PPTs.[3,11,39] Furthermore, a study comparing a range of human surrogate pain models has shown that intradermal capsaicin injection and HFS were characterized by pinprick hyperalgesia and mild thermal sensory loss, rather than by hyperalgesia to blunt pressure.[37] Moreover, a decrease in PPTs in the area of secondary hyperalgesia was not observed after topical application of capsaicin.[18,21] The present results support studies that did not find a decrease in PPTs.

4.2. No decrease in pressure pain thresholds at distant body sites

We found no evidence that HFS lowers PPTs at body sites more distant from the site of HFS. These results may suggest that CS, induced by the activation of skin nociceptors, does not involve a widespread mechanical pressure pain hypersensitivity. On the other hand, it could be argued that competing mechanisms (inhibition vs facilitation) are present simultaneously, and this would account for the fact that PPTs remained constant throughout the experiment. The repetition of stimuli can either lead to habituation or sensitization.[6,7,13] In our study, a potential increased sensitivity (ie, a decrease in PPTs) due to HFS might be

hidden by a habituation to repeated pressure pain stimuli (resulting in an increase in PPTs). However, previous studies have shown that PPTs do not habituate across repeated measurements,[5,10] provided that there is sufficient time between each measure,[11,26] which was the case in this study. Similarly, a decrease of PPTs may have been masked by the "pain inhibits pain" phenomenon referred to in humans as conditioned pain modulation.[42] However, this is also unlikely because conditioned pain modulation effects are known to quickly diminish after the end of the conditioning stimulus[12] and to be abolished after 15 minutes.[17] Note that our post-measurements were at 20 and 45 minutes after HFS.

Previous studies have also assessed PPTs at the temple after HFS.[34–36] In all 3 studies, the authors reported an increase in PPTs that was present immediately after HFS,[35] which persisted for at least 60 minutes[34] and up to 2 hours.[36] Importantly, there are some differences between this study and these previous studies. First, the authors of these previous studies mentioned that their HFS procedure induced ongoing sensations lasting up to 2.5 hours,[35,36] which may have influenced their measurements. In our study, we used a similar HFS electrode to the one originally described by Klein,[19] which does not induce any spontaneous ongoing sensation after HFS. Second, and contrary to our method, these studies[34–36] evaluated PPTs using single measures, instead of using the recommended arithmetic mean of 3 repeated measures.[1,5] Third, in these previous studies, besides measuring PPTs, they delivered other stimuli within the same session as well, whereas in our study, we only assessed PPTs (at T1 and T2).

We cannot, however, rule out that more prolonged nociceptive input (over weeks or months) may actually induce a widespread decrease in PPTs. Interestingly, Kronschläger et al.[22] recently showed that high-frequency electrical stimulation (HFS) of primary C-fiber afferents in rats triggers glial cell activation, which induces long-term potentiation at remote C-fiber synapses through the release of extracellular messengers, including D-serine and tumor necrosis factor that migrate through cerebrospinal fluid. The authors hypothesized that this gliogenic long-term potentiation may underlie widespread pain hypersensitivity in humans.

The results of previous studies suggest that input from muscles, fasciae, and skin induces different patterns of pain hypersensitivity.[28,40] In this study, HFS mainly activated cutaneous nociceptors and it could well be that intense or sustained nociceptive input originating from deeper tissues does induce a widespread decrease in PPTs.

To conclude, our study provides no evidence for the hypothesis that CS induced by the activation of skin nociceptors involves a widespread decrease in PPTs.

Disclosures

References

[1] Andersen S, Petersen MW, Svendsen AS, Gazerani P. Pressure pain thresholds assessed over temporalis, masseter, and frontalis muscles in healthy individuals, patients with tension-type headache, and those with migraine-a systematic review. PAIN 2015;156:1409–23.

[2] Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Drewes AM, Arendt-Nielsen L. Assessment and manifestation of central sensitisation across different chronic pain conditions animals to humans providing new options in development of therapies and profiling drugs under development. Eur J Pain 2017;22: 216–41.

[3] Balaguier R, Madeleine P, Vuillerme N. Is one trial sufficient to obtain excellent pressure pain threshold reliability in the low back of asymptomatic individuals? A test-retest study. PLoS One 2016;11: e0160866.

[4] Baumann TK, Simone DA, Shain CN, LaMotte RH. Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. J Neurophysiol 1991;66:212–27.

[5] Bisset L, Evans K, Tuttle N. Reliability of 2 protocols for assessing pressure pain threshold in healthy young adults. J Manipulative Physiol Ther 2015;38:282–7.

[6] van den Broeke EN, van Heck CH, Ceelen LAJM, van Rijn CM, van Goor H, Wilder-Smith OHG. The effect of high-frequency conditioning stimulation of human skin on reported pain intensity and event-related potentials. J Neurophysiol 2012;108:2276–81.

[7] van den Broeke EN, van Heck CH, van Rijn CM, Wilder-Smith OH. Neural correlates of heterotopic facilitation induced after high frequency electrical stimulation of nociceptive pathways. Mol Pain 2011;7:28.

[8] van den Broeke EN, Lenoir C, Mouraux A. Secondary hyperalgesia is mediated by heat-insensitive A-fibre nociceptors. J Physiol 2016;594: 6767–76.

[9] van den Broeke EN, Mouraux A. High-frequency electrical stimulation of the human skin induces heterotopical mechanical hyperalgesia, heat hyperalgesia, and enhanced responses to nonnociceptive vibrotactile input. J Neurophysiol 2014;111:1564–73.

[10] Chesterton L, Barlas P, Foster N, Baxter GD, Wright C. Gender differences in pressure pain threshold in healthy humans. PAIN 2003; 101:259–66.

[11] Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain 2007;23:760–6.

[12] Eitner L, Özgül S, Enax-Krumova EK, Vollert J, Maier C, Höffken O. Conditioned pain modulation using painful cutaneous electrical stimulation or simply habituation? Eur J Pain 2018;22:1281–90.

[13] Groves PM, Thompson RF. Habituation: a dual-process theory. Psychol Rev 1970;77:419–50.

[14] Gunnarsson H, Grahn B, Agerström J. Increased deep pain sensitivity in persistent musculoskeletal pain but not in other musculoskeletal pain states. Scand J Pain 2016;13:1–5.

[15] Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. J Clin Invest 1950;29:115–40.

[16] Henrich F, Magerl W, Klein T, Greffrath W, Treede R. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. Brain 2015;138:2505–20.

[17] Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice ASC. Reliability of conditioned pain modulation: a systematic review. PAIN 2016;157: 2410–19.

[18] Kilo S, Schmelz M, Koltzenburg M, Handwerker HO. Different patterns of hyperalgesia induced by experimental inflammation in human skin. Brain 1994;117:385–96.

[19] Klein T. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. J Neurosci 2004;24:964–71.

[20] Klein T, Stahn S, Magerl W, Treede RD. The role of heterosynaptic facilitation in long-term potentiation (LTP) of human pain sensation. PAIN 2008;139:507–19.

[21] Koltzenburg M, Lundberg L, Torebjörk HE. Dynamic and static components of mechanical hyperalgesia in human hairy skin. PAIN 1992;51:207–19.

[22] Kronschläger MT, Drdla-Schutting R, Gassner M, Honsek SD, Teuchmann HL, Sandkuhler J. Gliogenic LTP spreads widely in nociceptive pathways. Science 2016;354:1144–8.

[23] Lenoir C, Plaghki L, Mouraux A, van den Broeke EN. Quickly-responding C-fibre nociceptors contribute to heat hypersensitivity in the area of secondary hyperalgesia. J Physiol 2018;596:4443–55.

[24] Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. PAIN 2008;137:473–7.

[25] Nicholls M, Thomas N, Loetscher T, Grimshaw G. The Flinders Handedness survey (FLANDERS): a brief measure of skilled hand preference. Cortex 2013;49:2914–26.

[26] Nie H, Lars AN, Andersen H, Thomas GN. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. J Pain 2005;6:348–55.

[27] Pfau DB, Klein T, Putzer D, Pogatzki-Zahn EM, Treede RD, Magerl W. Analysis of hyperalgesia time courses in humans after painful electrical high-frequency stimulation identifies a possible transition from early to late LTP-like pain plasticity. PAIN 2011;152:1532–9.

[28] Schilder A, Magerl W, Hoheisel U, Klein T, Treede RD. Electrical high-frequency stimulation of the human thoracolumbar fascia evokes long-term potentiation-like pain amplification. PAIN 2016;157: 2309–17.

[29] Simone DA, Sorkin LS, Oh U, Chung JM, Owens C, LaMotte RH, Willis WD. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 1991;66:228–46.

[30] Smart K, Blake C, Staines A, Doody C. Clinical indicators of "nociceptive," "peripheral neuropathic" and "central" mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Man Ther 2010;15:80–7.

[31] Torta D, Van Den Broeke E, Filbrich L, Jacob B, Lambert J, Mouraux A. Intense pain influences the cortical processing of visual stimuli projected onto the sensitized skin. PAIN 2017;158:691–7.

[32] Torta D, Filbrich L, Broeke E, Legrain V. No perceptual prioritization of non-nociceptive vibrotactile and visual stimuli presented on a sensitized body part. Sci Rep 2018;8:5359.

[33] Treede RD. Gain control mechanisms in the nociceptive system. PAIN 2016;157:1199.

[34] Vo L, Drummond PD. Analgesia to pressure—pain develops in the ipsilateral forehead after high- and low-frequency electrical stimulation of the forearm. Exp Brain Res 2014;232:685–93.

[35] Vo L, Drummond PD. Coexistence of ipsilateral pain-inhibitory and facilitatory processes after high-frequency electrical stimulation. Eur J Pain 2014;18:376–85.

[36] Vo L, Drummond PD. High frequency electrical stimulation concurrently induces central sensitization and ipsilateral inhibitory pain modulation. Eur J Pain 2013;17:357–68.

[37] Vollert J, Magerl W, Baron R, Binder A, Elena EK, Geisslinger G, Gierthmühlen J, Henrich F, Hüllemann P, Klein T, Lötsch J, Maier C, Oertel B, Sigrid SH, Tölle T, Treede RD. Pathophysiological mechanisms of neuropathic pain: comparison of sensory phenotypes in patients and human surrogate pain models. PAIN 2018;159:1090–102.

[38] Wagenmakers EJ, Marsman M, Jamil T, Ly A, Verhagen J, Love J, Selker R, Gronau Q, Šmíra M, Epskamp S, Matzke D, Rouder J, Morey R. Bayesian inference for psychology. Part I: theoretical advantages and practical ramifications. Psychon Bull Rev 2018;25:35–57.

[39] Walton D, MacDermid J, Nielson W, Teasell R, Chiasson M, Brown L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. J Orthop Sport Phys Ther 2011;41:644–50.

[40] Witting N, Svensson P, Gottrup H, Arendt-Nielsen L, Jensen TS. Intramuscular and intradermal injection of capsaicin: a comparison of local and referred pain. PAIN 2000;84:407–12.

[41] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. PAIN 2011;152:S2–15.

[42] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611–15.