American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 7 (July), 2015: pp 595-605
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Effectiveness of High-Frequency Electrical Stimulation Following Sensitization With Capsaicin

Catherine R. Jutzeler,* Armin Curt,* and John L. K. Kramer*,†

**Spinal Cord Injury Center, University Hospital Balgrist, University of Zurich, Zurich, Switzerland.*
†School of Kinesiology, International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, British Columbia, Canada.

Abstract: Although nonnoxious, high-frequency electrical stimulation applied segmentally (ie, conventional transcutaneous electrical nerve stimulation [TENS]) has been proposed to modulate pain, the mechanisms underlying analgesia remain poorly understood. To further elucidate how TENS modulates pain, we examined evoked responses to noxious thermal stimuli after the induction of sensitization using capsaicin in healthy volunteers. We hypothesized that sensitization caused by capsaicin application would unmask TENS analgesia, which could not be detected in the absence of sensitization. Forty-nine healthy subjects took part in a series of experiments. The experiments comprised the application of topical capsaicin (.075%) on the left hand in the C6 dermatome, varying the location of TENS (segmental, left C6 dermatome, vs extrasegmental, right shoulder), and assessing rating of perception (numeric rating scale: 0–10) and evoked potentials to noxious contact heat stimuli. The extrasegmental site was included as a control condition because previous studies indicate no analgesic effect to remote conventional TENS. Conventional TENS had no significant effect on rating or sensory evoked potentials in subjects untreated with capsaicin. However, segmental TENS applied in conjunction with capsaicin significantly reduced sensation to noxious thermal stimuli following a 60-minute period of sensitization.

***Perspective:** The study indicates that sensitization with capsaicin unmasks the analgesic effect of conventional TENS on perception of noxious contact heat stimuli. Our findings indicate that TENS may be interacting segmentally to modulate distinct aspects of sensitization, which in turn results in analgesia to thermal stimulation.*

***Key words:** Transcutaneous electrical nerve stimulation, capsaicin, contact heat evoked potentials, experimental pain modulation.*

In healthy subjects, modulatory effects of transcutaneous electrical nerve stimulation (TENS) on experimental measures of pain (eg, thresholds) have been extensively investigated.[10,14,16,25,27,41,51] Although strongly supporting an analgesic effect on pressure pain thresholds,[10,11,32] evidence of thermal analgesia is more limited.[8,39] Owing to the specificity of segmental stimulation delivered at nonnoxious intensities, the analgesic effect of conventional TENS has been historically attributed to inhibition of pain signaling at the level of the spinal cord (ie, gate control theory of pain).[38,43,52] Compared to noxious counterirritation and recruitment of supraspinal structures involved in diffuse noxious inhibitory control, the use of nonnoxious high-frequency TENS represents a distinctly different approach to modulate pain through recruitment of large-diameter afferents. Although studies have confirmed the requisite anatomy and physiology to facilitate spinal interactions between A-beta and A-delta/C-fibers (eg, wide dynamic range neurons), other putative mechanisms of conventional TENS have been proposed to explain the

Received November 17, 2014; Revised February 16, 2015; Accepted March 13, 2015.
Supported by the Swiss National Science Foundation (SNF320030 135558) and the Clinical Research Priority Program "Neurorehab" of the University of Zurich, Switzerland. J.L.K.K. was supported by postdoctoral funding from the International Foundation for Paraplegia–Zurich.
The authors report no conflict of interests.
Address reprint requests to Catherine R. Jutzeler, MSc, Spinal Cord Injury Center, University Hospital Balgrist, Forchstrasse 340, 8008 Zurich, Switzerland. E-mail: cjutzeler@paralab.balgrist.ch
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2015.03.005

effectiveness of TENS in chronic pain states. Prominent among these is that electrical conditioning stimulation modulates neuropeptides and neurotransmitters involved in central and peripheral sensitization.[33-35]

Activating TRPV-1 receptors, capsaicin represents a well-known model of peripheral and central sensitization.[4,13,22] Following capsaicin application, animal studies have demonstrated upregulation of various neurotransmitters and neuropeptides in the dorsal horn, including those shown to be modulated by TENS.[20,23,53] Behaviorally, in humans, responses to capsaicin application are consistent with sensitization, in that sensitivity to noxious stimuli is increased (ie, pain thresholds are reduced).[4,31,44,55] Although capsaicin has been routinely applied in humans as an experimental model of pain,[22,31,42] translational studies examining the effect of conventional TENS after the induction of sensitization are currently lacking. The use of capsaicin to induce sensitization recognizes that TENS is typically not therapeutically applied in individuals with normal sensation and that modulation may depend on factors underlying the generation of pain symptoms; that is, TENS may behave differently in patients than in the healthy subjects. Pretreatment with capsaicin represents one step toward modeling chronic pain conditions, including those characterized by peripheral and central sensitization.[22,40,42]

The primary objectives of the proposed study were 2-fold. First, building on previous studies, we aimed to further assess the effectiveness of conventional TENS to reduce perception of noxious heat stimulation. More specifically, we were interested to examine the modulating effect of nonnoxious conventional TENS, investigating the potential for interactions between large- and small-diameter afferents in the spinal cord. For this purpose, responses to brief pulses of noxious contact heat stimulation were examined in healthy subjects before and after segmentally applied TENS (100 Hz at nonnoxious intensities). Second, we sought to address how sensitization might alter the effectiveness of conventional TENS to modulate perception of contact heat stimulation. Following the topical application of capsaicin (60 minutes), responses to contact heat and nonnoxious electrical stimulation were examined before and after segmental and extrasegmental TENS. The goal of testing different stimulation modalities (ie, contact heat and electrical stimuli) was to examine the specificity of TENS to modulate small-diameter, but not large-diameter, afferents. The working hypothesis was that if conventional TENS modulated sensitization, capsaicin would increase the effectiveness to alter perception of thermal stimulation.

Methods

Subjects

Forty-nine neurologically healthy subjects were included in the study (31 women, 18 men; mean age = 28.9 ± 6.6 years; range = 20–52 years). All subjects gave their written informed consent. The protocol was approved by the local ethics committee and was in accordance with the Declaration of Helsinki and approved by the local ethics committee (reference number: EK-04/2006).

Experimental Design

Study 1: Effects of Conventional TENS on Thermally and Electrically Evoked Pain

Subjects (n = 10) were examined with contact heat and electrical stimulation on the dorsum of the hand at the base of the thumb at 0, 10, 30, and 60 minutes and again after 10 minutes of conventional TENS. The purpose of repeatedly stimulating the hand before applying TENS was to ensure that the effect of TENS, applied at 60 minutes, was examined from a stable baseline (ie, reduce the potential effect of habituation on perception). To specifically address segmental effects (Fig 1A), TENS was applied in the area tested with contact heat and electrical stimulation (left hand, base of the thumb, within the innervation of the sixth cervical spinal segment). TENS

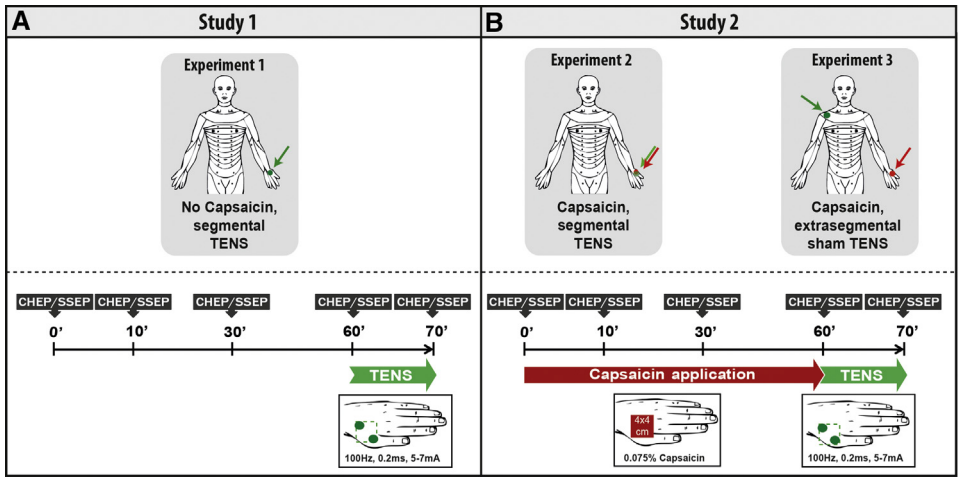

Figure 1. Study design. **(A)** In experiment 1, subjects underwent sessions of contact heat and electrical stimulations at 0, 5, 10, 30, and 60 minutes and again following 10 minutes of conventional TENS. TENS was applied in the area tested with contact heat stimulation. **(B)** Contact heat stimulation and electrical stimulation was examined during 60 minutes of topical application of capsaicin (baseline, 10, 30, and 60 minutes). After the final removal of capsaicin, 10 minutes of segmental (experiment 2, dorsum of left hand) or extrasegmental (experiment 3, shoulder) sham TENS was followed by the final examination of contact heat and electrical stimulations.