American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 5 (May), 2013: pp 538-548
Available online at www.jpain.org and www.sciencedirect.com

C-tactile Fibers Contribute to Cutaneous Allodynia After Eccentric Exercise

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Abstract: We recently showed that during acute muscle pain, C-tactile (CT) fibers mediate allodynia in healthy human subjects. In this study, we pursued the following questions: Do CTs contribute to allodynia observed in delayed onset muscle soreness (DOMS)? Is CT-mediated allodynia reproducible in a clinical pain state? In 30 healthy subjects, DOMS was induced in anterior compartment muscles of the leg by repeated eccentric contractions. DOMS was confirmed by mapping the emergence of tender points (decreased pressure pain thresholds). Furthermore, we measured pressure pain thresholds in a clinical subject who presented with activity-triggered heel pain but no resting pain. Cutaneous vibration (sinusoidal; 200 Hz–200 μm)—an otherwise innocuous stimulus—was applied to anterolateral leg before exercise, during DOMS, and following recovery from DOMS. The peripheral origin of allodynia was determined by employing conduction blocks of unmyelinated (intradermal anesthesia) and myelinated (nerve compression) fibers. In DOMS state, there was no resting pain, but vibration reproducibly evoked pain (allodynia). The blockade of cutaneous C fibers abolished this effect, whereas it persisted during blockade of myelinated fibers. In the clinical subject, without exposure to eccentric exercise, vibration (and brushing) produced a cognate expression of CT-mediated allodynia. These observations attest to a broader role of CTs in pain processing.

***Perspective:** This is the first study to demonstrate the contribution of CT fibers to mechanical allodynia in exercise-induced as well as pathological pain states. These findings are of clinical significance, given the crippling effect of sensory impairments on the performance of competing athletes and patients with chronic pain and neurological disorders.*

***Key words:** C fiber, allodynia, hairy skin, eccentric exercise, delayed onset muscle soreness, pressure pain threshold, intradermal anesthesia.*

Within the somatosensory system, stimulus encoding occurs peripherally at the receptor and is transmitted to higher-order neurons in a manner that allows us to readily differentiate among robust to subtle variations in a wide range of stimuli. However, in clinical conditions, we often observe a perceptual response that lacks compliance with stimulus characteristics, eg, touch-evoked pain. This phenomenon is known as allodynia. We recently showed that a rather abstruse class of low-threshold unmyelinated mechanoreceptors, termed C-tactile (CT) fibers, mediates vibration- and brush-evoked allodynia during acute (hypertonic saline-induced) muscle pain.[30,46] Conversely, in the absence of background pain, the activation of CT fibers correlates with a diffuse sensation of pleasant touch.[36] Therefore, background nociceptive input appears to play a crucial role in the production of CT-mediated allodynia. Nonetheless, it remains to be elucidated whether a perceptual level of pain is necessary to unmask the central effects of CT fiber inputs or whether the allodynic response can be elicited by subperceptual events. Furthermore, whether the expression of CT-mediated allodynia can be reproduced in a more persistent, or clinical, pain state remains to be tested.

To pursue these questions, we employed a natural form of muscle damage, termed delayed onset muscle soreness (DOMS), which can be evoked by unaccustomed eccentric exercise (weight bearing during muscle lengthening); downhill walking, for example. Following exercise, muscle

Received March 28, 2012; Revised December 23, 2012; Accepted January 7, 2013.
The National Health and Medical Research Council of Australia supported this work.
There are no conflicts of interest.
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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.01.009

soreness gradually develops; it usually peaks at 24 to 48 hours postexercise and invariably subsides within a week.[10,22,49] Although there need not be any resting pain following the onset of DOMS,[20,22,65] tenderness is often reported to palpation, contraction, and stretch in the affected muscles.[53] Muscle tenderness can be quantified by mapping the emergence of tender points (decreased pressure-pain thresholds [PPTs]) within the exercised muscles.[68,69] The mechanism of DOMS is poorly understood. Based on animal work, it was postulated that muscle fiber degeneration and necrosis were the primary features of eccentric exercise-induced damage.[16,17,34] However, recent studies in humans have indicated that myofiber degeneration and necrosis are not characteristic of DOMS,[71] and that it is in fact the adaptive remodeling of myofibers that has been considered to represent damage.[72] In addition, DOMS has been associated with inflammation with and without muscle damage as a primary event.[38,41,55]

Both muscle mechanoreceptors[2,68,69] and nociceptors[20,41,64] have been implicated in delayed soreness after exercise. Based on converging evidence, it is posited that the symptoms of DOMS, eg, a fall in mechanical threshold of exercised muscles, are an expression of central sensitization—in particular, changes at the level of the superficial dorsal horn.[65] What's intriguing is the dearth of information on the central effects of cutaneous inputs during DOMS, particularly given that CT fiber endings terminate densely in the superficial laminae of dorsal horn.[1,58,62] Furthermore, CT-mediated inputs have been shown to project to the limbic-emotional regions of the brain.[6,12] Whether the activation of CT fibers expresses allodynia during DOMS formed the focus of this study. DOMS was induced by eccentric exercise of the anterior compartment muscles of the leg. In addition, we investigated the contribution of CTs to allodynia in a clinical subject who reported no resting pain but in whom physical exertion evoked recurrent bouts of bilateral heel pain and induced a reversible alteration in gait (toe walking). Given that the postural adjustment, exhibited by the subject, mimics eccentric contractions of the anterior muscles of leg, we need not induce muscle damage experimentally in order to produce DOMS. Akin to our earlier work,[46] nerve conduction blocks were employed in order to determine the peripheral substrate of allodynia.

Some of the results have been published in abstract form.[44]

Methods

Thirty healthy human subjects (21 males and 9 females, aged 18–40 years) and a chronic pain patient (male, 19 years) took part in this study. Informed consent was obtained from each subject in writing. All experiments were approved by the University of Western Sydney Human Research Ethics Committee (approval number: H9190) and conformed to the principles of the Declaration of Helsinki. In each subject, the perceptual response to cutaneous vibration was examined just prior to eccentric exercise and once DOMS had set in. Furthermore, the peripheral neural substrate for realizing any change in the quality of vibration across preexercise and DOMS states was determined by employing nerve conduction blocks. While performing these tests, subjects sat comfortably on a chair with both legs horizontally stretched out and supported on both sides.

Cutaneous Vibration

A circular plexiglass probe (Australian Plastic Fabricators, Sydney, Australia) with a rounded 4-mm-diameter tip was placed perpendicular to the skin surface, overlying the anterior compartment muscles of leg, without compressing the underlying structures. Subjects were questioned to ensure that there was no discomfort at the site of contact. The probe was attached to a feedback-controlled sinusoidal stimulator.[40] The frequency (200 Hz) and amplitude (200 μm) parameters were chosen, as the resulting stimulus is normally innocuous and is capable of activating a range of cutaneous and subcutaneous mechanoreceptors,[40,43,46] not to mention the mechanical impedance of the skin being at its lowest at this frequency.[60] Each period of vibration lasted 30 seconds and was repeated at 45-second intervals in order to avoid desensitization of the activated fiber classes. The interstimulus interval of 45 seconds conforms to the recovery time for CT fiber fatigue in humans ($\sim$30 seconds),[37,70] in addition to the stimulation intervals followed in recent psychophysical and microneurography studies on this afferent class.[36] Furthermore, such an interval provided sufficient time to perform sensory tests in order to track the progression of nerve conduction blocks. Moreover, it is consistent with our earlier findings in an acute model of pain,[46] which showed that the CT-mediated response can overshoot the stimulus duration, but invariably dissipates within a 45-second interval (see also[13,29,75]). Brown noise was delivered through headphones to ensure that auditory cues associated with the vibrotactile stimulator were not provided.[43]

Delayed Onset Muscle Soreness

DOMS was induced in the anterior compartment muscles of the lower limb by slow, repeated plantarflexions of the foot (10 times per set; 9 sets in total). The generation of DOMS was confirmed by systematically mapping the emergence of tender points (decreased PPTs) within the exercised muscles using a force gauge with a 1-cm^2 rubber tip (Pain Test algometer; Wagner Instruments, Greenwich, CT). To ensure muscle loading during plantarflexion, the entire body weight was borne on the experimental leg (single leg stance) with the subject standing on a 15-cm-high metal platform at hind foot level and inclining toward the wall.[19,20] A 2.25-kg weight belt was strapped to the distal leg in order to apply a greater load on the stretched muscles.[68] Prior to the induction of DOMS, a 2- $\times$ 2-cm grid comprising 30 points was drawn on the skin overlying the targeted muscles, as shown in Fig 1. The minimal pressure required to produce detectable pain was measured at each grid point in a randomized pattern across a range of intensities (5–30 N, in multiples of 5).[69]