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An Illusion of Proximal Radiation of Pain Due to Distally Directed Inhibition

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Abstract: The perceived site of pain can frequently radiate from the site of tissue injury. However, the mechanisms supporting spatial aspects of cutaneous pain radiation remain poorly understood. Such mismatches between the actual location and the perceived location of stimuli are also found across other somatosensory modalities. During simultaneous innocuous stimulation at multiple sites, proximal stimuli are perceived as more intense than distal stimuli. To determine if pain radiates in a predominantly proximal direction, 20 subjects rated pain intensity from simultaneously applied pairs of noxious (49°C) thermal stimuli. Proximal and distal stimuli were each rated separately. As the distance between probes was decreased, pain from the proximal site increased relative to that arising from the distal site. Comparisons between paired stimuli and single control (49°C) stimuli revealed that pain arising from the distal stimulus site was inhibited. This distally directed inhibition produced an illusion that pain radiates in a proximal direction. The proximal radiation/distal inhibition of pain observed in the present investigation may represent a perceptual "copy" of neural information used to modulate withdrawal responses. Thus, supraspinally mediated responses to pain can be coordinated with spinally mediated withdrawal reflexes.

Perspective: ***Radiation of pain is a perplexing clinical problem. The present findings indicate that the perceived location of pain may be shaped by inhibitory as well as facilitatory processes.***

Key words: *Referred pain, inhibitory, psychophysics.*

Clinical pain can be perceived at remote areas far from its origin,[1,16-18] and this can cause equivocation on diagnosis and treatment failure.[5,11,26] Mismatches between the perceived and actual location of stimulation have been reported across multiple somatosensory modalities.[7,9,13,20,30] For example, during tactile stimulation on the forearm or the palm of the hand, subjects consistently perceive the stimulus to be more proximal than its actual location.[2] Similarly, innocuous electrical or radiant heat stimuli applied on the forearm are also perceived more proximally than the actual stimulus site.[13,40] During chemical stimulation with capsaicin, subjects first mislocalize sensations distally, but later their percept shifts to produce a proximal mislocalization similar to that of tactile stimulation.[9] Finally, in classic studies of electrical stimulation–induced hyperalgesia, the zone of altered sensation is markedly asymmetric. Hyperalgesia extends in a proximal direction from the electrical stimulus while simultaneously a zone of hypoalgesia extends distally from the stimulus site.[10]

The perceived magnitude of proximal stimuli can also be amplified by distal stimuli. For example, during innocuous electrocutaneous stimulation, subjects feel more frequently that both electrodes (cathode and anode) were activated when the cathode was at a distal position than when it was at a proximal location.[12] Anecdotal observations suggest that a similar proximal radiation of pain occurs during simultaneous noxious stimulation with multiple probes[29] (unpublished observations). However, such radiation remains poorly characterized and has not been examined in a prospective fashion.

The purpose of the present investigation was to quantitatively assess the degree of proximal radiation of pain. To better understand the mechanisms supporting the proximal radiation of pain, we examined 1) the influence of stimulus separation distance on radiation, 2) potential

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differences in pain sensitivity along the proximal-distal axis and, 3) possible inhibition of pain arising from the distal stimulus during paired (proximal + distal) thermal stimulation.

Methods

Subjects

All subjects participating in this study (10 men and 10 women) were healthy, pain- and drug-free volunteers between the ages of 20 and 39 years (average, 26.4 years). Fifteen subjects were white (7 women and 8 men), 1 woman was Asian, 1 man was Hispanic, and 3 subjects were black (2 women and 1 man). All subjects gave written, informed consent acknowledging that they would experience experimental painful stimuli, that all methods and procedures were clearly explained, and that they were free to withdraw from the experiment at any time without prejudice. Subjects (n = 20) participated in the first session involving stimulation of the leg, and 16 returned approximately 4 months later for the second session involving stimulation of the arm. All procedures were approved by the Institutional Review Board of Wake Forest University School of Medicine.

Stimulation Paradigms

All thermal stimuli were delivered with TSA II devices (Medoc, Ramat Yishai, Israel), using 16 × 16-mm stimulus probe(s). All stimuli were 5 seconds in duration and used rise-and-fall rates of 4°C/s. Stimuli were delivered to the left arm or the left leg by a single probe (control) or by 2 probes simultaneously. Paired stimuli were separated by 10, 20, 30, and 40 cm on the leg and by 5, 10, 20, and 30 cm on the arm to evaluate effects of distance on the spatial integration of pain. Paired stimuli were electronically synchronized and monitored on a digital chart recorder (PowerLab/4sp; AD Instruments, Inc., Colorado Springs, CO). Stimulator parameters were fine-tuned to ensure that both probes delivered nearly identical stimuli simultaneously. To further reduce confounds due to slight differences in stimulus delivery between probes, the probe location (proximal/distal) was counterbalanced within subjects. To minimize sensitization or habituation, stimuli were delivered to marked sites in a predetermined spatial fashion (total of 55 sites along the leg or arm), and only 2 stimuli were given to any 1 site. A minimal interval of 30 minutes was given between application of stimuli at the same area and 30 seconds between any two consecutive stimuli to avoid long-term suppression or sensitization of nociceptive afferents.[28] Moreover, both stimulus intensities and probe separation distances were randomized to avoid order effects.

Two temperatures were used in all experimental trials: 35°C as baseline (neutral thermal stimulus) and 49°C as the noxious thermal stimulus. The 49°C stimulus temperature was chosen since frankly noxious stimuli elicit a high frequency of reports of pain radiation.[30] Paired stimuli consisted of three different conditions: 49°C proximal/49°C distal (49°Cp/49°Cd), 49°C proximal/35°C distal (49°Cp/35°Cd), and 35°C proximal/49°C distal (35°Cp/49°Cd). Single (ie, nonpaired) 49°C control stimuli were also applied at all stimulated sites along the leg (or arm) to control for differences in sensitivity across body regions and to evaluate possible interactions between paired stimuli. Perceived pain from a single 49°C stimulus also was compared with paired stimuli rated separately, and by this comparison, spatial summation or inhibition involving multiple stimuli could be assessed. The length of each session was approximately 2 hours. Three (single) or 4 (paired) trials were used for each condition (distance × combination of probes).

Psychophysical Assessment and Training

Pain intensity and pain unpleasantness were rated with separate mechanical visual analog scales (VAS).[31,32,37] These 15-cm–long sliding scales were anchored with the words "no pain sensation"–"the most intense pain imaginable" and "not unpleasant at all"–"the most unpleasant imaginable." After subjects slid the scale to the appropriate level that corresponded to their actual pain perception, pain ratings were quantified by a labeled numeric index (0 to 10 range) on the back of the scale (out of the subject's view). In the first set of training stimuli, a single probe delivering different temperatures (from 35°C to 49°C) was used to give subjects experience rating pain intensity and pain unpleasantness. In the second set of training stimuli using the right leg, pairs of noxious stimuli separated by 10 cm were delivered by using only the 2 temperatures (35°C and 49°C) used in the experiment. The number of paired stimuli used in the second training was not fixed. Instead, each subject received a certain number of trials until she or he felt comfortable performing the task. On average, subjects received 14 stimuli during this process. These training stimuli allowed subjects to gain experience in providing separate ratings of 2 stimuli delivered simultaneously.

During the experimental phase, whenever paired stimuli were presented, subjects were instructed to separately attend to both probes and rate the pain from each one of the stimuli (noxious or neutral stimuli) on each trial. Thus, subjects separately rated pain intensity and unpleasantness for proximal and distal sites after each trial. Similar designs have been used to assess spatial summation of pain; however, in those studies, instead rating the individual stimuli, subjects were required to rate overall pain from the 2 stimuli.[34,35] To control for multisensory interactions, subjects were required to fix their eyes on the midpoint between the probes during the time that stimuli were delivered.

Statistical Analyses

The 2 assessed aspects of pain (intensity and unpleasantness) were highly similar, so for clarity, analyses focused only on pain intensity. For each subject, VAS ratings were first averaged across the 3 to 4 presentations of each condition (stimuli × distance). Using repeated-measures analyses of variance, averaged VAS ratings of paired test stimuli (49°Cp/49°Cd; 35°Cp/49°Cd; 49°Cp/