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Topically applied capsaicin inhibits sensitivity to touch but not to warmth or heat-pain in the region of secondary mechanical hyperalgesia

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Abstract

The aim of this study was to investigate tactile sensitivity near the site of primary hyperalgesia evoked by capsaicin applied topically to the dorsolateral aspect of the hand. In the first experiment (N = 15), touch thresholds increased in the fifth finger ipsilateral to the topically applied capsaicin, but remained unchanged at greater distances from the site of capsaicin treatment. In a second experiment (N = 12), the effect of the capsaicin treatment on sensations evoked not only by light touch but also by warmth, heat-pain, and pressure-pain to a 2-mm diameter steel probe was investigated in the fifth finger. Again, tactile sensitivity was inhibited at the fifth finger, even though stimulation with a cotton bud evoked no discomfort; moreover, sensitivity to warmth and heat-pain were unimpaired. However, sensitivity to pressure-pain increased in the fifth finger after the capsaicin treatment, possibly due to activation of nociceptors sandwiched between the probe tip and bone that normally responded to sharp stimuli. These findings suggest that the central mechanisms that mediate secondary mechanical hyperalgesia suppress sensitivity to innocuous tactile sensations. This effect may contribute to tactile hypoesthesia in chronic pain conditions.

Keywords: Capsaicin, mechanical hyperalgesia, thermal hyperalgesia, allodynia, tactile hypoesthesia

Introduction

Even in the absence of primary afferent nerve dysfunction, chronic pain is often associated with sensory impairment (Moriwaki et al. 1994; Moriwaki and Yuge 1999; Leffler et al. 2000a). Moreover, in conditions such as complex regional pain syndrome, sensory impairment may extend well outside the region of injury and pain—sometimes in a hemilateral distribution (Thimineur et al. 1998; Rommel et al. 1999, 2001; Drummond and Finch 2006).

Similar effects, although on a smaller scale, have been reproduced in human experimental pain models (Apkarian et al. 1994; Bolanowski et al. 2000; Leffler et al. 2000b; Magerl and Treede 2004). For example, heating the thenar eminence to levels that induced pain was found to suppress local vibrotactile perception independently of shifts in attention or arousal (Apkarian et al. 1994). Sensitivity of the thenar eminence to vibratory stimuli also decreased after noxious heat was applied to the dorsomedial forearm and wrist (Bolanowski et al. 2000). In another study of healthy volunteers, the site of intradermal injection of 40 μg capsaicin in the forearm was surrounded by an area of sensitivity to pinprick stimuli (secondary hyperalgesia) which, in turn, was surrounded by an area of reduced sensitivity to light touch (tactile hypoesthesia) (Magerl and Treede 2004). Similarly, tactile sensitivity decreased in the area of referred pain (generally the upper arm) after an injection of hypertonic saline into the infraspinatus muscle (Leffler et al. 2000b).

These effects suggest an association between tactile hypoesthesia and the spinal and supraspinal mechanisms that sensitize responses to noxious stimulation (Moriwaki et al. 1994; Moriwaki and Yuge 1999; Bolanowski et al. 2000; Magerl and Treede 2004). However, noxious heat or intradermal injections of capsaicin or hypertonic saline could also release inflammatory products in the skin that interfere with normal sensory processing (e.g., pro- or anti-inflammatory cytokines) (Saade et al. 2002; Angst et al 2008). Thus, the aim of the present study was to determine whether topically applied capsaicin, which is mildly painful but does not evoke tissue injury or inflammatory mediator release (Reilly and Green 1999), would produce local tactile hypoesthesia near the site of primary hyperalgesia in healthy subjects. An additional aim was to determine whether topical capsaicin

interfered with the perception of stimuli in other sensory modalities near the site of application. As secondary hyperalgesia is more prominent for mechanical than thermal stimulation (Raja et al. 1984), it was hypothesized that hypoesthesia near the site of capsaicin application would be more prominent for mechanical than thermal stimuli.

Materials and methods

Participants

The sample consisted of 7 men and 20 women aged between 18 and 52 years who were free of chronic pain. The experiments were conducted in accordance with the Declaration of Helsinki. Each subject provided their informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee. Neither the experimenter nor the participants were aware of the hypotheses under investigation.

Procedures

The procedures were administered in a temperature-controlled room maintained at 21 ± 1°C. The site of capsaicin application (the dorsal aspect of the right hand in the distribution of the ulnar nerve, Figure 1) was cleaned with soap and water and an alcohol swab. A solution containing 0.02 M capsaicin (0.6%) was prepared by dissolving capsaicin powder (Sigma, Sydney, Australia) in 50% ethanol in water (Culp et al. 1989). Three hundred µl of this solution was placed on the gauze pad of an elastic dressing (2.0 cm × 2.5 cm), which was applied to the cleaned skin. The dressing was covered with plastic tape to retard evaporation of the capsaicin solution. After 30 min, the dressing was removed and the residual capsaicin was washed from the skin with soap and water.

In 15 participants, calibrated nylon monofilaments (Semmes-Weinstein aesthesiometer, Stoelting, Chicago, IL, USA) were used to investigate tactile sensitivity before the capsaicin was applied and shortly after it was washed from the skin on the dorsal aspect of the first, third, and fifth fingers of each hand (within, respectively, the distal distribution of the radial, median, and ulnar nerves) just

proximal to the base of the fingernail (Figure 1). The sites were tested 4 times with each filament at 5- to 10-s intervals. Participants closed their eyes and were instructed to identify the site of stimulation if they noticed a sensation. The sequence started with filament 2.44 (nominal bending force log[10 × 2.44] mg). Sufficient force was applied to bend the filament for 1 s. Stronger filaments (3.22, 3.84, 4.08, 4.56, and 5.64) were then used as required, until participants were able to detect at least 50% of trials with the same filament (the touch threshold). Test administration took approximately 15 min. At the conclusion of testing, pain at the capsaicin-treated site averaged 4.7 ± 2.2 (SD) on a 1–10 verbal rating scale where 1 corresponded to “no pain”, 5 to “moderate pain”, and 10 to “extremely intense pain”.

In another 12 participants, touch thresholds were investigated in the fifth finger before and after the application of capsaicin, as described above. In addition, warmth and heat-pain thresholds were investigated in the same region with a thermocouple-controlled radiant heat lamp (Figure 1). Skin temperature increased from 30°C at 0.5°C/s to 48°C or until the participant signalled warmth or heat-pain. Pressure-pain thresholds were investigated in the fifth finger with a purpose-built 1-mm radius steel probe with a hemispheric tip that was linked to a pressure sensor. Pressure of application was monitored on a digital display and was increased at a constant rate by the experimenter until it was perceived as painful. The warmth, heat-pain, and pressure-pain thresholds were defined as the average of three trials. Allodynia around the site of capsaicin application was also mapped out by dragging a cotton wool bud slowly across the hand toward the capsaicin-treated site (Figure 1). The participant was asked to report when the sensation changed from light touch to discomfort. Sensitivity to touch was investigated first, followed by tests of sensitivity to pressure-pain, warmth, and heat-pain. Test administration took 20–25 min. At the conclusion of testing, pain at the capsaicin-treated site averaged 5.2 ± 2.2 (SD) (i.e., moderately painful) on the 1–10 verbal rating scale described above.

Statistical approach

In the first group of subjects, touch thresholds were investigated in Time (before vs. after the application of capsaicin) × Side (ipsilateral vs. contralateral to capsaicin) × Site (first, third, or fifth finger) repeated measures analyses of variance. In the second group, touch, warmth, heat-pain, and

pressure-pain thresholds were investigated in separate Time (before vs. after the application of capsaicin) × Side (ipsilateral vs. contralateral to capsaicin) repeated measures analyses of variance. A value of $p < 0.05$ was considered to be statistically significant.

Results

In the second group of subjects, the touch threshold again increased in the fifth finger ipsilateral to the topically applied capsaicin [interaction between Time and Side, $F(1, 11) = 34.1$, $p < 0.001$] (Figure 3A). In contrast, pressure-pain thresholds initially were high but *decreased* in this finger after the capsaicin treatment, consistent with the development of mechanical hyperalgesia [interaction between Time and Side, $F(1, 11) = 73.8$, $p < 0.001$] (Figure 3B). Both before and after the capsaicin treatment, warmth thresholds were higher on the right side than the left [main effect for Side, $F(1, 11) = 8.75$, $p < 0.05$] (Figure 3C); in addition, thresholds decreased at both sites after the capsaicin application [main effect for Time, $F(1, 11) = 16.0$, $p < 0.01$]. Similarly, heat-pain thresholds were higher on the right side than the left both before and after the topically applied capsaicin [main effect for Side, $F(1, 11) = 7.74$, $p < 0.05$] (Figure 3D); however, heat-pain thresholds did not change significantly at either site after the capsaicin application. Allodynia to the movement of a cotton bud across the skin was detected between 5 and 30 mm around the site of capsaicin application. However, as sites of sensory testing in the fifth finger were greater than 50 mm from the capsaicin-treated site, stimulation with the cotton bud evoked no discomfort at these sites.

Discussion

Sensitivity to mechanical stimulation and heat generally increases at sites of cutaneous inflammation and tissue injury. This primary hyperalgesia is mediated, at least in part, by an increased excitability of primary afferent nociceptors (Culp et al. 1989; LaMotte et al 1992). Surrounding the site of primary hyperalgesia is a zone of heightened sensitivity to punctate stimuli (secondary hyperalgesia),

and discomfort can sometimes be evoked within this zone by lightly brushing the skin (allodynia). The tenderness surrounding the region of primary hyperalgesia is mediated by sensitization of spinal neurons that transmit nociceptive impulses within the central nervous system (LaMotte et al.

1991; Simone et al. 1991; Torebjork et al. 1992). In particular, allodynia appears to involve sensitization of spinal neurons that receive input from low-threshold mechanoreceptors (LaMotte et al. 1992; Kilo et al 1994), whereas sensitization of spinal neurons that are activated by nociceptive A-δ fibres mediates hyperalgesia to punctate stimuli (Ziegler et al. 1999; Magerl et al, 2001; Klede et al 2003). Allodynia is generally less extensive and resolves more rapidly than hyperalgesia to punctate stimuli (LaMotte et al. 1991), implying greater excitation of spinal wide dynamic range neurons by convergent nociceptive than non-nociceptive input. In the present study, central sensitization probably mediated discomfort evoked by gentle tactile stimulation around the site of capsaicin application.

Hyperalgesia to blunt pressure applied over soft tissue in the forearm or leg is limited to the area of primary hyperalgesia (Kilo et al. 1994). Nevertheless, sensitivity to pressure increased several cm from the site of capsaicin application and surrounding allodynia in the present study, in a region of the dorsal finger comprising a thin layer of skin over bone. Pressure applied to skin appears to evoke nociceptive activity in deep tissues (e.g., muscle or bone) rather than the skin, because topical application of local anaesthetic cream does not increase pressure-pain thresholds (Kosek et al. 1995). Tonic pressure applied to human skin increases activity in initially mechanically insensitive nociceptors in proportion to ratings of pain (Schmidt et al. 2000). Repetition of the tonic stimulus results in more intense pain and sensitization of these nociceptors, similar to the sensitization evoked by intracutaneous capsaicin injection (Schmelz et al. 2000). The blunt probe employed in the present study may have evoked mechanical hyperalgesia in the secondary zone (normally evoked by punctate rather than blunt stimuli) because pressure applied to the thin layer of skin overlying bone was more effective at inducing nociceptor discharge than applying pressure over soft tissue. For example, the blunt probe might have assumed a “sharp” quality for cutaneous tissues sandwiched between the probe tip and bone, due to activation of A-δ nociceptors that respond to punctate stimuli (Ziegler et al. 1999; Magerl et al 2001; Klede et al. 2003). In any case, hyperalgesia most likely was mediated by

spinal nociceptive neurons sensitized by input originating at the site of capsaicin application (LaMotte et al. 1991; Simone et al 1991; Torebjork et al 1992) as the hyperalgesia was limited to the capsaicin-treated side.

Like previous studies that employed thermal stimuli at or below the heat-pain threshold (Hardy et al. 1950; Raja et al 1984; LaMotte et al 1991; Kilo et al 1994; Ali et al 1996), neither the warmth nor heat-pain threshold differed between sites of secondary mechanical hyperalgesia and control sites in the present study. However, in certain circumstances hyperalgesia to heat appears to develop after a delay in the zone of secondary mechanical hyperalgesia (e.g., Sumikura et al. 2003, 2005). It depends on characteristics such as the duration and intensity of the heat stimulus (Sumikura et al. 2005), and may involve both peripheral sensitization of nociceptive C-fibres and central sensitization to input from nociceptive A-δ fibres (Sumikura et al. 2005). Increased sensitivity to warmth was detected in both hands after the capsaicin application, possibly reflecting a learning effect or peripheral sensitization with repeated testing (Leffler et al. 200b).

Magerl and Treede (2004) identified a zone of tactile hypoesthesia that extended beyond the region of secondary hyperalgesia induced by an intradermal injection of capsaicin. Similarly, heat-evoked pain in the forearm was found to suppress sensitivity to vibratory stimulation in the thenar eminence (Bolanowski et al. 2000). This tactile hypoesthesia was not merely due to distraction because it was limited to a region around the site of capsaicin injection (Magerl and Treede 2004) and was induced by painful stimulation at some forearm sites but not others (Bolanowski et al. 2000). Similarly, in the present study, both tactile hypoesthesia and mechanical hyperalgesia were evoked by the topical application of capsaicin. The hypoesthesia was detected within the same peripheral nerve distribution as the topically applied capsaicin (the ulnar nerve) but did not develop in adjacent median or radial nerve territories. While this implies that the tactile hypoesthesia was limited in its distribution to a single nerve territory, this explanation is not consistent with experimental findings (Bolanowski et al. 2000; Magerl and Treede 2004) or clinical observations which suggest that spinal and supraspinal mechanisms mediate tactile hypoesthesia (Moriwaki et al. 1994; Moriwaki and Yuge 1999). It is unlikely that inflammatory products influenced the development of tactile hypoesthesia in the present

study because the flare induced by topical capsaicin treatment is not associated with inflammatory mediator release (Reilly and Green 1999).

Sensitivity to heat increases initially at the site of capsaicin administration whereas touch thresholds and sensitivity to pain induced by mechanical stimulation do not change (Simone and Ochoa 1991). Conversely, desensitization to the repeated application of capsaicin is associated with decreases in sensitivity to heat-pain but no change in touch thresholds or sensitivity to painful mechanical stimulation (Simone and Ochoa 1991; Fuchs et al 2000). *In vitro* studies on a rat hindpaw skin–saphenous nerve preparation have confirmed that polymodal C-fibre afferents are sensitive to capsaicin whereas C-fibres responsive only to mechanical stimulation are insensitive to capsaicin (Seno and Dray 1993). Similarly, polymodal A-δ fibres are activated by capsaicin whereas mechano-sensitive A-δ fibres are not. Together, these findings indicate that capsaicin does not directly affect the threshold of mechano-sensitive fibres. Magerl and Treede 2004) reported that the sensory nerve action potential provoked by local electrical stimulation around the site of intradermal capsaicin injection was unimpaired. Thus, nerve conduction in the A-β fibres that relay information about light tactile stimulation to the central nervous system apparently remained intact in the hypoesthetic skin. Magerl and Treede postulated that impulse traffic from capsaicin-sensitive C-fibres inhibited spinal mechanoreceptive input, perhaps via inhibitory presynaptic connections with A-β fibres (Janig and Zimmermann 1971). If so, this could compromise tactile sensitivity and promote allodynia and secondary hyperalgesia.

Alternatively, supraspinal mechanisms could contribute to the tactile hypoesthesia that sometimes develops at sites remote from the source of pain (Moriwaki and Yuge 1999; Rommel et al. 1999). Somatosensory cortical responsiveness to innocuous stimuli diminishes in painful conditions such as carpal tunnel syndrome (Tecchio et al. 2002) and complex regional pain syndrome (Pleger et al. 2005, 2006). Tactile sensitivity may improve following relief of chronic pain (Moriwaki and Yuge 1999). Moreover, treatments that inhibit pain also reverse the somatosensory cortical deficit (Maihofner et al. 2004) in line with improvements in tactile sensitivity (Pleger et al. 2005). These observations suggest that persistent pain suppresses activity in regions of the primary somatosensory cortex that normally

respond to innocuous tactile sensations (Apkarian et al. 1992). This inhibitory process may extend well beyond the receptive fields of the activated nociceptive neurons (Moriwaki et al. 1994; Moriwaki and Yuge 1999; Bolanowski et al. 2000).

With the possible exception of the hands, pain perception appears to be symmetrical (Sarlani et al. 2003; Schaffner et al. 2008). When differences are detected, the left hand generally is more sensitive to pain than the right (Wolff et al. 1965; Brennum et al. 1989; Chandramouli et al. 1993; Sarlani et al. 2003), even in subjects with left-hand dominance (Lugo et al. 2002). In the present study, all but two of the participants were right-handed. Before the capsaicin application, the left hand was more sensitive to pressure-pain than the right (Brennum et al. 1989); moreover, the left hand was more sensitive to thermal stimulation than the right both before and after the capsaicin application (Lugo et al. 2002; Sarlani et al. 2003). The mechanism of asymmetry in pain perception is uncertain, but perhaps reflects asymmetry of pain modulation processes or cortical processing which focus attention on infrequent (but thereby behaviourally relevant) sensations of pain in the left hand (Wolff et al. 1965; Coghill et al. 2001; Symonds et al 2006).

One limitation of the approach used in the present study was that pain and secondary hyperalgesia subsided fairly rapidly after the topical application of capsaicin. Because of the time constraints that this imposed, examination was limited to a single modality or location several cm from the capsaicin treatment. Nevertheless, the capsaicin-treated site was still moderately painful at the conclusion of both studies. In previous reports, tactile hypoesthesia was distributed 6–7 cm around the site of capsaicin injection (Magerl and Treede 2004), whereas heat-pain to the dorsomedial forearm inhibited vibro-tactile sensitivity 21 cm away in the thenar eminence (Bolanowski et al. 2000). Curiously, however, heat applied to the volar aspect of the forearm did not affect the vibratory threshold even though this was the same distance from the thenar eminence. Bolanowski et al. (2000) suggested that this discrepancy may be related to somatotopic organization, as the dorso-medial forearm is in the same dermatome as the thenar eminence whereas the volar forearm is in a different dermatome.

In summary, tactile hypoesthesia was detected in the fifth finger after capsaicin was applied to the dorsolateral aspect of the hand, but not in more medial fingers. Factors that influence the extent of

tactile hypoesthesia (e.g., the location, modality, intensity, and duration of the nociceptive stimulus, and the distribution and persistence of secondary hyperalgesia) require further investigation. In particular, it would be interesting to determine whether secondary hyperalgesia evoked by persistent widely distributed experimental pain could result in the hemilateral pattern of tactile hypoesthesia and other sensory disturbances seen in complex regional pain syndrome (Rommel et al. 1999, 2001; Drummond and Finch 2006), and whether the hypoesthesia disappears at the same time that the secondary hyperalgesia resolves.

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Figure 1. Site of capsaicin application (black box) and sites of sensory testing. In the first 15 participants, sensitivity to light touch was investigated in the first, third, and fifth fingers of each hand with calibrated nylon monofilaments (von Frey hairs). In the other 12 participants, sensitivity to light touch was investigated in the fifth finger of each hand. In addition, warmth, heat-pain, and pressure-pain thresholds were investigated at these sites, and allodynia to light stroking was delineated around the site of capsaicin application.

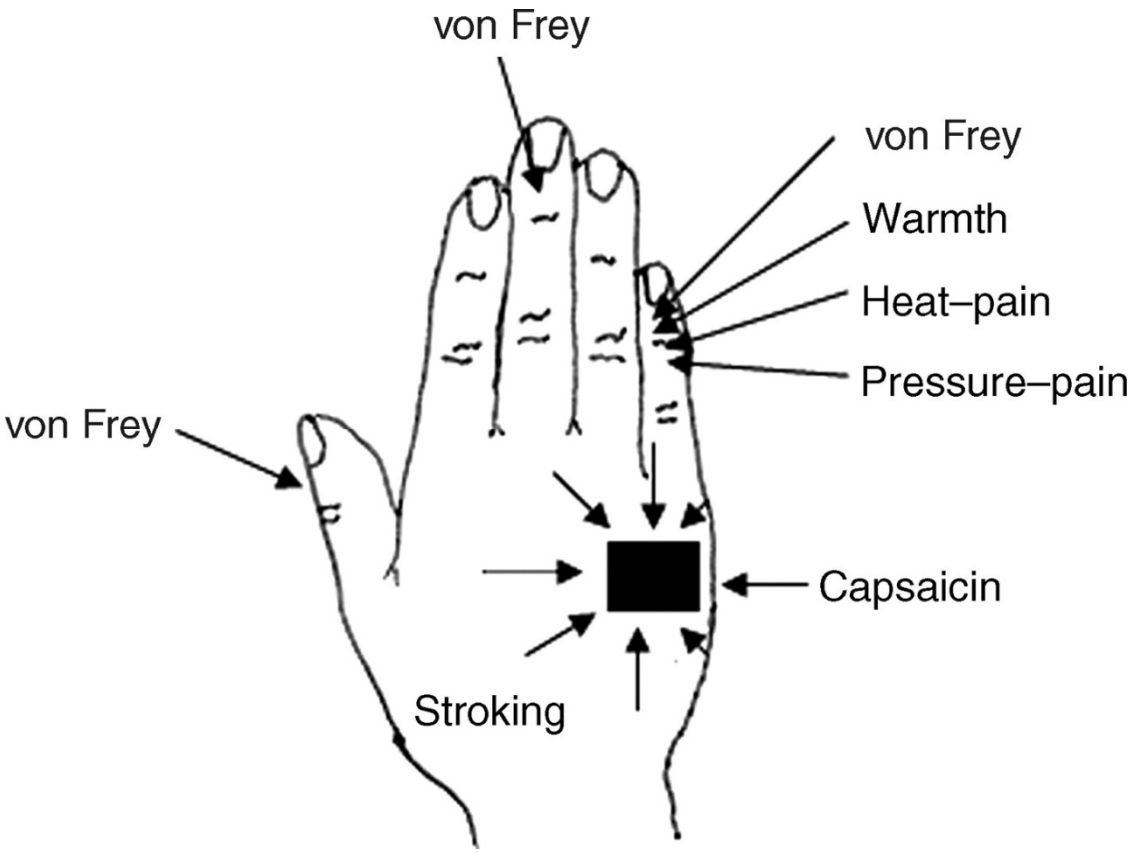

Figure 2. Touch threshold (±SE) in the fingers before and after the topical application of 0.6% capsaicin on the dorsolateral aspect of the right hand. The touch threshold increased in the fifth finger ipsilateral to the topically applied capsaicin (*$p < 0.001$ after Bonferroni correction, compared to the threshold before capsaicin and to the threshold contralateral to the topically applied capsaicin), but did not change at any other site.

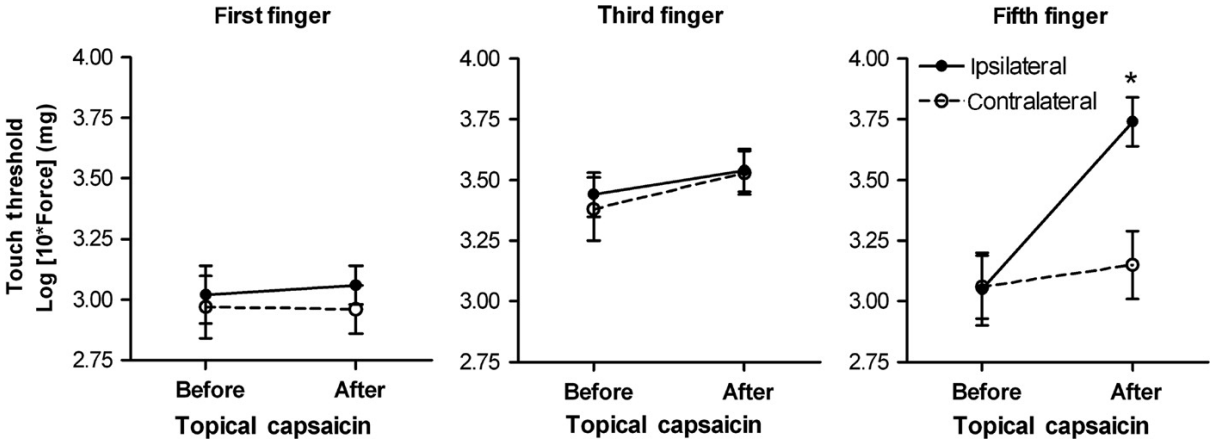

Figure 3. Sensory thresholds (±SE) in the fifth finger before and after the topical application of 0.6% capsaicin. (A) The touch threshold increased ipsilateral to the topically applied capsaicin (*$p < 0.001$ compared to the threshold before capsaicin and to the threshold contralateral to the topically applied capsaicin). (B) Before the capsaicin application, the pressure-pain threshold was greater on the right (capsaicin-treated) side than the left (*$p < 0.05$), and decreased ipsilateral but not contralateral to the capsaicin application (#$p < 0.001$). (C) The warmth threshold decreased on both sides after the capsaicin application, and generally was higher on the right side than the left. (D) The heat-pain threshold was higher on the right side than the left but did not change significantly after the capsaicin application.