Capsaicin-evoked Mechanical Alldynia and Hyperalgesia Cross Nerve Territories

Evidence for a Central Mechanism

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Background: The finding in some patients with neuropathic pain that mechanical allodynia (pain evoked by light touch) and hyperalgesia (supranormal pain evoked by painful stimuli) extend beyond the territory of a single nerve or spinal sensory root (extraterritorial pain) often prompts a diagnosis of psychiatric illness. The hypothesis that focal nociceptive input in a single nerve territory can result in allodynia and hyperalgesia in a nerve territory adjacent to the input was investigated in normal human subjects.

Methods: On separate days, 13 healthy volunteers each received left radial and ulnar nerve blocks. After block of either nerve, sensation remaining for three classes of afferents (Aβ, low-threshold mechanoreceptors, Aδ nociceptors, and C-polymodal nociceptors) allowed inference of the nerve territory of the adjacent nerve, and the area of overlapping innervation. On a third day, 1,000 μg intradermal capsaicin was administered into a site such that C-nociceptor input was confined to the ulnar nerve territory. Areas of brush allodynia and pinprick hyperalgesia were determined.

Results: Spread of brush allodynia beyond all three borders of the ulnar nerve territory occurred in 9 of 13 patients (for these subjects, range 5–28 mm), whereas spread of pinprick hyperalgesia beyond all borders of the ulnar nerve territory occurred in 12 of 13 subjects (range 1–31 mm). Spread of brush allodynia beyond the Aβ border of the ulnar nerve territory occurred in 10 of 13 subjects (range 4–35 mm); and spread of pinprick hyperalgesia beyond the Aδ border of the ulnar nerve territory occurred in 12 of 13 subjects (range 1–31 mm).

Conclusions: It is concluded that activation of C-nociceptors evokes a state of central sensitization that may manifest itself by the appearance of extraterritorial pain abnormalities. (Key words: Measurement techniques: sensory testing. Nerves: blockade. Pain, allodynia: capsaicin-evoked. Pain, hyperalgesia: capsicain-evoked.)

FOR more than one hundred years, physicians have been taught to regard paralysis or anesthesia in an anatomic impossibility unilateral glovelike or stockinglike distribution as a cardinal sign of hysteria, because this did not fit the distribution of any motor or sensory nerve.¹ Patients with chronic pain after focal peripheral nerve damage or tissue injury sometimes report that they have spontaneous pain, hyperalgesia, and allodynia in a glovelike or stockinglike distribution, and this may also prompt a psychiatric diagnosis. Walters’ described the traditional view of pain, which does not follow nerve territories or dermatomes as ”psychogenic regional pain,” with ”attributes of a hallucination . . . a sensory perception with no peripheral stimulus.”¹ Even clinicians within the field of pain research often categorize such patients as having a psychiatric rather than a physiologic basis for their symptoms.³ This is based on the view that painful sensory symptoms in neuropathy are explained solely by peripheral mechanisms, such as sensitization of nociceptors, and should follow the anatomic distribution of peripheral nerves or posterior roots.

However, recent evidence from animal studies suggests that extraterritorial pain may be a consequence of sensitization of central nervous system neurons. For example, in rats with an experimental painful mono-neuropathy of the sciatic nerve, light touch evokes pain (mechanical allodynia) not only in the territory of the injured nerve but also in the adjacent uninjured saphenous nerve territory.¹,⁵

The current study demonstrates similar mechanisms in neurologically normal human volunteers with experimen-
tial pain. Intradermal injection of the chemoinnervant capsaicin evokes an intense burning pain that is known to be mediated by C-fiber nociceptors. After such an injection, gentle stroking or brushing of the skin evokes mechanical allodynia, and a pinprick evokes an exaggerated pain sensation (hyperalgesia) from wide areas surrounding the injection site. The capsaicin-evoked allodynia and hyperalgesia are qualitatively very similar, if not identical, to the symptoms observed in some patients with painful peripheral neuropathies.

To evaluate the hypothesis that central nervous system sensitization accounts for the spread of mechanical allodynia and hyperalgesia into an adjacent nerve territory in human subjects, we administered intradermal capsaicin after first defining the borders of both the ulnar nerve and the adjacent radial nerve territories on the dorsum of the left hand.

Materials and Methods

With participants' informed consent and approval by our Institutional Review Board, we studied 13 medication-free healthy volunteers (aged 23–47 yr) with no history of systemic disease or chronic pain. Subjects were unaware of the study's hypothesis and were instructed to avert their gaze during stimulation.

Under uniform conditions and on two separate days, each subject underwent radial and ulnar nerve blocks. Each radial nerve block was performed at the elbow by inserting a 1.5-inch, 22G short-beveled needle halfway between the lateral edge of the biceps tendon and the lateral border of the arm, perpendicular to the skin and toward the humerus. A paresthesia was sought before injecting 5–10 ml 1.5% lidocaine. Each ulnar nerve block was performed at the wrist by inserting a 1.5-inch, 22G short-beveled needle just lateral to the tendon of the flexor carpi ulnaris. A paresthesia was sought before injecting 3–5 ml 1.5% lidocaine.

Because the distribution of innervation may vary for different classes of primary afferents, separate innervation borders for the three fiber classes were determined: first, Aβ/low-threshold mechanoreceptive afferents (AβLMs); second, Aδ high-threshold mechanoreceptive afferents; and third, C-fiber polymodal nociceptors. Aδ low-threshold mechanoreceptive afferent innervation was mapped by stroking the skin with a #2 flat Princeton watercolor brush at standard pressure (bending the distal 2 mm of the brush) and rate of 1 cm/s. Aδ high-threshold mechanoreceptive afferent innervation was determined using a standard safety pin pressed against the skin until dimpling was visible. C-fiber polymodal nociceptor innervation was mapped using a series of 0.5 μg (0.005 ml of 0.1 mg/ml solution) intradermal capsaicin (8-methyl N-vanillyl-4-homolog); Fluka, Ronkonkoma, NY), dissolved in 15% Tween 80, emulsified in sterile water for injection. This method takes advantage of capsaicin's selective excitation of C-fibers. Both pinprick and capsaicin stimuli were administered in a 1 mm × 1 mm grid pattern. For each stimulus, the site of application progressed from the anesthetic area toward the area of intact sensation on the dorsum of the hand.

Sensations remaining after block of the radial nerve allowed us to infer the ulnar nerve territory, and vice versa, and also delineated the zone of overlapping innervation. After each nerve block, borders and visible landmarks (e.g., veins and nevi) were marked on the skin and transferred onto both a latex glove and an acetate transparency.

In a third session, 1,000 μg (0.1 ml of 10 mg/ml solution) intradermal capsaicin was administered into the ulcer area 1.5 cm beyond the border of the radial nerve's C polymodal nociceptor territory, resulting in a bleb smaller than 1 cm in diameter in all subjects. Thus, peripheral nociceptor input was confined to the ulnar nerve territory. The site of intradermal capsaicin injection was determined with the latex glove on, then marked through the glove onto the skin. Capsaicin was injected after the glove was removed, without any markings other than the injection site remaining on the hand.

The dose of capsaicin used here (1,000 μg) is considerably larger than the largest dose (100 μg) used by others. The largest experiments in our laboratory showed that the size of the secondary zone increases with doses in the range of 250–1,000 μg. With all doses, the secondary zone approximates an elongated oval with the long diameter aligned proximally. Extraterритори spread from the territory of the ulnar nerve to that of the radial nerve would have to occur transversely, in the direction of the oval's short diameter. We chose the dose to obtain the largest possible spread in this direction.

Areas of brush-evoked allodynia and pinprick-evoked hyperalgesia were determined every 5 min for 60 min. Skin temperature was kept within 0.2º of 36°C by a radiant heat lamp. Monitored with a cutaneous thermistor placed on the skin between the second and third metacarpophalangeal joints. The spread of the

Anesthesiology, V 85, No 3, Sep 1996
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areas of brush allodynia and pinprick hyperalgesia are presented as the mean ± SEM distance from the site of injection, as measured along the transverse axis on the surface of the hand.

To evaluate the possibility that the capsaicin-Tween emulsion might disperse from the site of injection into the adjacent nerve territory and directly sensitize nociceptors in that territory, 13 subjects were administered approximately the same volume of intradermal capsaicin as was administered in the third session (0.05-0.1 ml, 0.1 mg/ml) in the presence of an ulnar nerve block, into the insensate region 1 cm from the inferred radial nerve border. Lack of spontaneous pain, allodynia, or hyperalgesia over the area of remaining sensation would indicate that capsaicin remains confined to the insensate area and does not spread beyond 1 cm into the adjacent nerve territory. We evaluated these subjects for 30-60 min until the conduction block resolved.

To evaluate the possibility that the intradermal injection of capsaicin might cause expansion of the associated nerve territory, six subjects returned for radial nerve block with 10 ml of 2% lidocaine and, as soon as they demonstrated complete sensory blockade to brush and pinprick, 1,000 µg intradermal capsaicin injected at approximately the same site as before. After the capsaicin injection, the borders of remaining sensation (i.e., the ulnar nerve territory as defined by brush and pinprick) and the borders of the areas of allodynia and hyperalgesia were measured every 5 min for 60 min.

Results

After nerve blocks, the areas of skin unresponsive to Aδ/βLTМ fiber stimulation were consistently larger than the areas of skin unresponsive to both Aδ fiber stimulation (mean distance from Aδ/βLTМ border, 5.2 ± 0.5 mm) and C fiber stimulation (mean distance from Aδ/βLTМ border, 5.1 ± 0.5 mm). Regions anesthetic to all (Aδ/βLTМ, Aδ, and C) fiber stimulation in a typical subject are illustrated in figure 1A. The inferred nerve territories are illustrated in figure 1B; as expected, the radial and ulnar nerve territories overlapped. Along the transverse axis of the dorsal hand, at the level of the capsaicin injection, the mean overlap of Aδ/βLTМ fiber innervation was 9.1 ± 8.5 mm, the mean overlap of Aδ fiber innervation was 17.5 ± 9.1 mm, and the mean overlap of C fiber innervation was 16.4 ± 9.9 mm.

As has been noted previously, subjects described the intradermal capsaicin injection as evoking intense burning pain, and all had an associated focal area of hypoesthesia at the site of injection (approximately 1 cm in diameter) surrounded by wide areas of pain to stimulation with brush and pinprick. Among all subjects, the mean transverse spread from the site of injection toward the radial nerve territory was 31.6 ± 3.1 mm for the area of brush allodynia and 41.2 ± 3.1 mm for the area of pinprick hyperalgesia. Mean maximum spread of mechanical allodynia occurred at 16.5 (range 5-30) mm; mean maximum spread of pinprick hyperalgesia occurred at 23.8 (range 10-55) mm.

Spread of brush allodynia beyond the borders of all borders (Aδ/βLTМ, Aδ, and C) of the ulnar nerve territory occurred in 9/13 patients, while spread of pinprick hyperalgesia beyond all borders of the ulnar nerve territory occurred in 12 of 13 patients (fig. 1C and fig. 2). The mean extraterritorial spread (all borders) was 11.2 ± 7.8 mm (range 5-28 mm) for brush allodynia (n = 9) and 15.9 ± 10.4 mm (range 1-31 mm) for pinprick hyperalgesia (n = 12).

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Spread of brush allodynia beyond the Aδ/βLTМ border of the ulnar nerve territory occurred in 10 of 13 subjects; spread of pinprick hyperalgesia beyond the Aδ border of the ulnar nerve territory occurred in 12 of 13 subjects. Of these subjects, the mean transverse spread of brush allodynia beyond the ulnar Aδ/βLTМ territory was 14.7 ± 2.9 (range 4-35 mm), and the mean transverse spread of pinprick hyperalgesia beyond the ulnar Aδ territory was 15.7 ± 2.9 mm (range 1-31 mm). Twelve of the 13 patients developed some degree of extraterritorial spread of either brush allodynia or pinprick hyperalgesia (fig. 2).

In the presence of an ulnar nerve block, we administered 0.05-0.1 ml (0.1 mg/ml) of intradermal capsaicin into the insensate area, 1 cm from the border of sensation or the inferred radial nerve border (determined by sensory testing for Aδ, Aδ, and C fiber innervation). No subject complained of spontaneous pain, allodynia, or hyperalgesia in any area of the hand for the duration of the conduction block (30-60 min of testing).

Localization of the border of the ulnar nerve territory was highly reproducible. In the six subjects who returned 104 ± 9.6 days later for repeat blocks and capsaicin injections, radial nerve blocks resulted in variation of the brush border location of 2.7 ± 2.3 mm, and variation of the pinprick border location of 2.5 ± 1.8 mm. In all six subjects, there was no change in the insensate area, and the borders of the allodynia and
Fig. 1. Nerve territories and spread of brush allodynia in subject 4. (A) Region insensitive to all (Aβ low-threshold mechanoreceptive afferents, Aδ high-threshold mechanoreceptive afferents, and C-fiber polymodal nociceptors) fiber stimulation after radial nerve block (right of dashed line), and region insensitive to all fiber stimulation after ulnar nerve block (left of dashed-dotted line). The area between these distributions is the zone of overlap. (B) Ulnar (left of dashed line), radial (right of dashed-dotted line), and overlapping nerve territories inferred from (A). The dorsal surfaces of the 2nd, 3rd, and half of the 4th digits are innervated by the median nerve. (C) Spread of brush allodynia into the adjacent radial nerve territory after intradermal injection of capsicain into the ulnar nerve territory (ulnar nerve territory, dashed line; radial nerve territory, dashed-dotted line; site of intradermal capsicain injection, O) which approximates the size of the bleb; area of brushing allodynia is enclosed by continuous line.

Hyperalgesic areas did not expand into the territory of the blocked radial nerve during the 60 min that followed the capsicain injection (data not shown).

Discussion

The intradermal capsicain injection produced a local stimulation of C-nociceptors with widespread mechani-
cal allodynia and hyperalgesia in the normal skin surrounding the injection site (the secondary zone). Two classes of explanation have been advanced to explain the development of mechanical allodynia and hyperalgesia in the secondary zone after capsicain: (1) sensitized nociceptors, and (2) central nervous system changes that “misinterpret” Aβ low-threshold mechanoreceptor input as painful and amplify the response to nociceptor input.

At least some capsicain-sensitive C-fiber nociceptors have receptive fields comprising widely branching intratocutaneous terminal arbors. It has been proposed that there is a population of such nociceptor that mediate the brush-evoked allodynia and pinprick-evoked hyperalgesia in the secondary zone surrounding an intradermal capsicain injection. The effect may be either direct or indirect. In the hypothesized direct effect, one of the nociceptor’s terminal branches lies at or near the injection site, and its exposure to capsicain causes its terminal branches in the secondary zone to become sensitized to mechanical stimulation. No evidence has been found for such an effect, despite extensive searches in monkeys and humans. In our subjects, the administration of the capsicain-Tween emulsion at least 1 cm outside the radial nerve border did not result in spontaneous pain, mechanical allodynia, or hyperalgesia in the radial nerve territory, indicating that there was no direct nociceptive input in that territory that might have resulted from dispersion of capsicain from the site of injection. For each of the 13 subjects, lack of mechanical allodynia in the radial territory was associated with a normal spread of brush allodynia. In the present experiment, the branches of the ulnar nerve were left for sensitization in the normal skin. However, experiments have never shown that capsicain is sensitized by exposure to the skin.

Human skin is innervated by nociceptors in intradermal capsicain; however, intradermal capsicain showed that some nociceptors are not sensitized by exposure to the skin. In the present experiment, the branch of the ulnar nerve was left for sensitization in the normal skin. However, experiments have never shown that capsicain is sensitized by exposure to the skin.

Fig. 2. Extension of allodynia and hyperalgesia beyond all fiber borders of the ulnar nerve territory for each subject. Subject 4 is represented by the square. The origin corresponds to the ulnar nerve territory border (all fiber types). Negative numbers correspond to those secondary zones that remained within the ulnar nerve territory. Extraterritorial mechanical allodynia or hyperalgesia failed to develop in only one subject. Extraterritorial hyperalgesia but not allodynia developed in three subjects.
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jicts, lack of mechanical allodynia over the radial nerve territory was assessed for well beyond the time to maximal spread of brush-evoked allodynia in the main experiment. In the hypothesized indirect effect, the distal branches release a substance that induces mechanical sensitization in the terminals of other nociceptors. However, experiments in humans and monkeys have never shown a nociceptor becoming sensitized when capsaicin is injected well outside of its receptive field.

Human skin is innervated by several kinds of C-fiber nociceptors and the responses of some of these to intradermal capsaicin injections have not yet been tested thoroughly. In particular, a recent report shows that some human C-fiber nociceptors have receptive fields comprising active and inactive terminal branches. The inactive branches are sensitized by the direct application of chemoinnervants (mustard oil or capsaicin), but there seems to be little or no effect on the inactive branch when the irritants are applied to the skin innervated by the active branch. Our demonstration that the border of the ulnar nerve territory remained stable after a capsaicin injection indicates that sensitized inactive branches cannot account for the spread of allodynia and hyperalgesia into the adjacent nerve territory. More generally, our data show that any explanation for the secondary zone that relies exclusively on the properties of primary afferent neurons must demonstrate how such properties can account for extraterritorial spread.

Afferent fibers from different neurons mingle in the common spinal nerves and posterior roots, and their cell bodies mingle in the dorsal root ganglia. It has been shown in experimental animals that abnormal cross talk between axons and cell bodies develops after severe nerve injury. It seems highly unlikely that such phenomena develop in normal human subjects within minutes of a capsaicin injection. We thus reject cross talk as an explanation for the extraterritorial spread reported here.

In contrast to the difficulties encountered by theories based on peripheral mechanisms, several lines of evidence, including the data reported here, indicate that the altered sensitivity of the secondary zone surrounding an intradermal capsaicin injection is owing to central nervous system mechanisms. For example, microneurographic studies in humans have shown that the brush allodynia of the secondary zone is evoked by activity in AδLTM, afferents whose activation normally evokes only innocuous tactile sensations. Data from experiments in monkeys indicate that an intradermal capsaicin injection sensitizes nocireponsive neurons in the spinal cord dorsal horn such that their response to AβLTM and nociceptor input is amplified. An intradermal injection of capsaicin evokes discharges from C-fiber nociceptors with receptive fields at the injection site. Animal experiments show that C-fiber nociceptor barriques sensitize spinal cord dorsal horn nocireponsive neurons such that their response to both nociceptor and AβLTM input is amplified. This C-fiber-evoked central sensitization is at least partly due to activation of glutaminergic receptors of the N-methyl-D-aspartate type. One would thus predict that the capsaicin-evoked secondary zone in human subjects would be inhibited by pharmacological blockade of N-methyl-D-aspartate receptors, and data supporting this prediction have been reported.

There are several parallels between the sensory abnormalities in the capsaicin-evoked secondary zone and the mechanical allodynia and hyperalgesia that are seen in some patients with chronic pain after nerve or soft tissue injuries. Many of these cases are preceded by a painful event or condition that generates C-fiber nociceptor input (e.g., a partial nerve lesion in causalgia, soft tissue trauma in reflex sympathetic dystrophy, and a painful attack of shingles preceding postherpic neuralgia). At least some of these patients have mechanical allodynia that is evoked by activity in AβLTM, and areas of mechanical allodynia that likely extend beyond the nerve territory of the presumed nociceptive input. Moreover, there is a growing body of evidence to show that N-methyl-D-aspartate receptor blockade relieves the pain of these patients, which is consistent with the hypothesis that patients have N-methyl-D-aspartate receptor-mediated central sensitization. The validation of capsaicin as a model of pain mediated by a central mechanism supports its use in humans for the initial screening of new drugs thought to reverse central sensitization before clinical trials.

Many spinal cord nocireponsive neurons receive input from more than one nerve or spinal root. It thus follows that C-fiber nociceptor-evoked central sensitization will produce abnormalities of pain sensation in areas that need not correspond to territories of nerves or dermatomes. The data presented here show that such a phenomenon can be demonstrated in neurologically normal human subjects. The same physiologic processes may explain similar phenomena in patients with nerve or soft tissue injury. Thus, both organic and psychogenic mechanisms must be considered in...
the differential diagnosis of chronic pain with extraterritorial spontaneous pain, allodynia, and hyperalgesia.

The authors thank Des. Daniel Keshlalo, Jr. and Robert Caudle for reviewing the manuscript.

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