Neural Mechanisms of Hyperalgesia After Tissue Injury

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For more than 25 years, investigators from APL and the Johns Hopkins School of Medicine have collaborated on research aimed at understanding the neural mechanisms of pain sensation. This research is based on correlating results from studies of pain sensations in humans with results from studies of neural activity in anesthetized animals. One aspect of pain that has clinical importance is hyperalgesia—the enhanced pain to stimuli applied to the skin that develops after tissue injury and in certain diseases. We review here the neural mechanisms of hyperalgesia. Primary hyperalgesia, which develops at the site of tissue injury, is associated with an increased sensitivity of the peripheral nerve fibers involved in pain. Secondary hyperalgesia, which develops in uninjured tissue surrounding the site of injury, exhibits symptoms similar to those seen in chronic pain patients and is caused by an enhanced neural responsiveness in the central nervous system.

INTRODUCTION

Pain serves as a warning system to protect an organism from injury and is one of the main reasons that patients go to physicians. In most cases, treatment of the underlying injury or disease ameliorates the pain, but for some, the pain persists well after the disease or injury has been cured. This persistent pain is called chronic pain and does not serve a useful biological function.

APL has been interested in a form of chronic pain called neuropathic pain. In this disease, pathology in the nervous system leads to chronic pain. The pathology can be caused by a disease (e.g., diabetes, shingles, AIDS) or trauma to the nerve (e.g., from a bullet or knife wound). Patients with neuropathic pain complain of ongoing pain as well as enhanced pain sensitivity to stimuli applied to their skin. For example, lightly touching the skin can be extremely painful in some patients with neuropathic pain. We call this increased pain sensitivity hyperalgesia (from the Greek, hyper = above, algos = pain).

As an example, an elderly woman in otherwise good health experiences the sudden onset of a localized region of shooting pain in the left side of the chest, starting from the midline in the back and radiating toward the front. Two days later she notices an inch-wide band-like red rash with scattered small blisters in the same region of the back and chest (Fig. 1a). She consults her physician, who diagnoses her condition as an acute attack of shingles (herpes zoster) and tells her that her symptoms should subside in a few days and that the skin lesions will heal in 2–3 weeks. Six months later, the patient continues to have pain and hypersensitivity in the
chest; the area of pain now extends to involve a large area on the back (Fig. 1b). Even brushing the skin with a cotton swab is painful, as are clothes or sheets rubbing against her skin in the affected region. Thus, a localized region of pain associated with an episode of shingles has resulted in a widespread area of intense pain and hyper-sensitivity such that even touch and pressure are painful. This phenomenon of hyperalgesia characterizes many of the chronic pain states associated with disease or injury that affect the peripheral or central nervous system.

Hyperalgesia also develops after injury to the skin. Most readers are familiar with the enhanced pain that develops after a sunburn; just the rubbing of fabric against the skin and gentle warming from a shower cause discomfort. The hyperalgesia that develops after skin injury is similar in many aspects to the hyperalgesia that develops in neuropathic pain. Studies of hyperalgesia after skin injury therefore provide a human surrogate for studies of hyperalgesia in neuropathic pain. In this article, we briefly review the mechanism of hyperalgesia that develops after an injury to the skin, focusing mainly on changes which occur in the peripheral nervous system that may account for the hyperalgesia.

**TWO FORMS OF HYPERALGESIA**

When a natural stimulus (e.g., heat) is applied to the skin, there is a range of stimulus intensities over which the stimulus is not painful. As the stimulus intensity is increased, however, a stimulus level is eventually reached where the stimulus becomes painful. Above this level, pain increases with stimulus intensity. A hypothetical stimulus-response function is shown in Fig. 2. When the skin is injured and hyperalgesia develops, this stimulus-response function is shifted to the left, resulting in a lowering of the pain threshold and an increase in pain to suprathreshold stimuli. We seek to determine what in the nervous system can account for this leftward shift in the stimulus-response function.

Injury to the skin (e.g., from a burn) can lead to the development of two forms of hyperalgesia (Fig. 3). Primary hyperalgesia develops at the site of the injury, Secondary...
hyperalgesia develops in the uninjured tissue that surrounds the injury. The characteristics of primary and secondary hyperalgesia differ. In the area of primary hyperalgesia, there is hyperalgesia to both mechanical and heat stimuli. In contrast, in the area of secondary hyperalgesia, there is hyperalgesia to mechanical stimuli but not to heat stimuli. This dichotomy suggests that the neural mechanisms of primary and secondary hyperalgesia differ.

Primary Hyperalgesia

In one of our early studies to investigate the mechanisms of primary hyperalgesia, we applied a controlled burn injury to the hand. The injury was produced by a 53°C heat stimulus applied for 30 s using a laser thermal stimulator system developed at APL (see the boxed insert below). This stimulus produced intense pain and resulted in a blister several hours later in about half of the subjects (Fig. 4).
MEASUREMENTS OF PAIN

Several techniques are available to assess the intensity of pain in humans. A common method is the visual analog scale (VAS), in which verbal descriptors of pain are placed along a scale and subjects mark the scale at a level corresponding to their pain (Fig. A). Subjects use a mouse to move the bar up and down the scale, and ratings are digitized at fixed time points. A method we have used often because it is amenable to correlation with neurophysiological data is the magnitude estimation technique. Here, subjects assign an arbitrary number (e.g., 10) to the intensity of pain associated with a standard stimulus (e.g., 45°C) and rate the intensity of subsequent stimuli relative to this modulus. For example, if the next stimulus was twice as painful as the standard stimulus, subjects would report twice the value of the modulus (i.e., 20 in this example) or half as painful, half the modulus (i.e., 5 in this example). Thus, all ratings are based on a ratio with respect to the modulus. The data in Fig. B were collected from human subjects in response to heat stimuli. The first stimulus was always 45°C. The remaining stimuli ranged from 41°C to 49°C and were presented to the terminals of C-fiber nociceptors in anesthetized monkeys (Fig. B). A skin incision was made along the course of the peripheral nerve of interest, and the nerve was dissected from connective tissue. A longitudinal slit was made in the tissue surrounding the nerve trunk, and a small bundle of nerve fibers was cut away from the nerve and rotated onto a dissection platform. Under an operation microscope, the nerve bundle was teased apart with jewelers’ forceps to obtain fine filaments with only a few nerve fibers. A small filament was placed on a silver wire electrode, and neural activity was recorded using a low-noise differential amplifier. Neural activity consisted of impulses of electrical signals called action potentials. The skin in the distribution of the monkey nerve under study was squeezed until a region was found where squeezing evoked a response in one of the nerve fibers on the recording electrode. Nylon monofilaments were bent at a force that depended on the filament diameter. We used calibrated monofilaments of different diameters to determine the threshold force to achieve a response. Subsequent mechanical, thermal, and chemical stimuli were then applied at or near the receptive field.

Data from the human psychophysical experiments and the monkey neurophysiological experiments were normalized by dividing by the response to the first stimulus. The close correlation in the stimulus-response functions for the human pain ratings and the CMH responses provide strong evidence that heat pain is signaled by activity in these nerve fibers. Note in Fig. B that the normalized response to the 45°C stimulus delivered as part of the random sequence is much less than 1, reflecting the pronounced fatigue that occurs to repeated heat stimulation at short interstimulus intervals (in this case, 30 s).
rate the intensity of pain to these heat stimuli. Before injury, the pain threshold was around 45°C and pain ratings increased monotonically with stimulus intensity above pain threshold (Fig. 5a). A marked hyperalgesia to heat developed after the burn injury as was evident by a leftward shift in the stimulus-response function. There was a decrease in pain threshold and an increase in pain to suprathreshold stimuli. For example, the 41°C stimulus was not painful before the injury. After the injury, however, the 41°C stimulus was more painful than the 49°C stimulus was before injury.

What accounts for this primary hyperalgesia to heat that develops at the site of injury? Are there changes in the response properties of the nerve fibers that go to the area of injured skin? To address these questions, we recorded the neural activity from single nerve fibers in the peripheral nerve of an anesthetized monkey (see "Measurements of Pain"). We recorded from two classes of peripheral nerve fibers called A-fibers and C-fibers. This classification is based on the speed at which signals in the nerve fibers propagate from the periphery to the spinal cord; A-fibers are myelinated and propagate at fast conduction velocities (2–50 m/s), whereas C-fibers are unmyelinated and propagate at slow conduction velocities (0.5–2.0 m/s). We were particularly interested in nerve fibers that had receptors in the skin responding to intense, noxious stimuli (i.e., “nociceptors,” from the Latin, noco = to injure, hurt). Nociceptors are thought to provide the peripheral signal for pain sensation. We recorded neural activity from nociceptors that responded to both mechanical and heat stimuli: AMHs (A-fiber mechano-heat–sensitive nociceptors) and CMHs (C-fiber mechano-heat–sensitive nociceptors).

The average responses of AMHs and CMHs to heat stimuli before and after the burn injury are shown in Figs. 5b and 5c, respectively. We first focus on the response of the CMHs. Before the injury, as noted previously (Fig. 5c), the threshold for response is around 45°C, and the response increases monotonically with stimulus temperature. The stimulus-response function of the CMHs (Fig. 5c) correlates well with the pain ratings before injury (Fig. 5a) and provides evidence that CMHs...
encoded the pain to heat before injury. After injury, the stimulus-response function of the CMHs is shifted to the right. The threshold is higher, and the response to suprathreshold stimuli is decreased. This is opposite to what would be expected from the observed pain ratings and suggests that CMHs do not provide the neuronal signal for heat hyperalgesia from the injury site.

Now consider the AMHs. Before injury, most AMHs do not respond to heat over the range of temperatures tested (Fig. 5b). However after injury, there is a marked sensitization in the heat response. The threshold for response is lowered and the magnitude of the response to suprathreshold stimuli is increased. These results provide evidence that sensitization of AMHs accounts for the primary hyperalgesia to heat that develops after an injury.

These studies were done on the glabrous (i.e., non-hairy) skin of the hand. Burn injuries to the hairy skin of the arm also lead to hyperalgesia to heat. However, in contrast to glabrous skin, burn injuries to hairy skin cause a sensitization of both CMHs and AMHs. We currently do not know what accounts for this difference. Regardless, in general, primary hyperalgesia is thought to be due to an enhanced responsiveness or sensitization of the nociceptors that signal pain.

Secondary Hyperalgesia

Secondary hyperalgesia develops after a wide range of cutaneous injuries including burns, mechanical trauma, and freeze injuries. One technique to produce secondary hyperalgesia that is used by a number of investigators is to inject a small volume (10 μL) of capsaicin into the skin. Capsaicin is the active ingredient in hot peppers and produces intense pain upon injection. Once the pain disappears, a large area of flare and secondary hyperalgesia becomes apparent (Fig. 6).

The flare, or reddening of the skin, is due to a dilation of the blood vessels in the skin and lasts for about 30 min. The activation of nociceptors by capsaicin leads to the release of substances, called neuropeptides, from the terminals of the nociceptors. These neuropeptides cause vasodilation. The release of neuropeptides is not restricted to the site of capsaicin injection. It also occurs in other terminals of these nociceptors outside the injection area. Excitation of one part of the receptor by capsaicin leads to the propagation of signals to other parts of the receptor and the release of the neuropeptides. The large area of the flare, relative to the area to which capsaicin was applied, reflects the large area over which these particular nociceptors have terminals.

Two forms of secondary hyperalgesia to mechanical stimuli are observed (Fig. 6). **Stroking hyperalgesia** occurs in response to gentle stroking of the skin with soft stimuli (e.g., a Q-tip). This is sometimes called dynamic hyperalgesia because it involves a moving stimulus. **Punctate hyperalgesia** occurs in response to punctate mechanical stimuli such as a pin or a nylon monofilament. Punctate hyperalgesia is sometimes called static hyperalgesia because it involves applying a stimulus to a fixed position for a period of time.

The characteristics of stroking and punctate hyperalgesia differ. The area of stroking hyperalgesia is smaller than the area of punctate hyperalgesia. In addition, the duration of stroking hyperalgesia is short (e.g., about 30 min after capsaicin injection), whereas the duration of punctate hyperalgesia is long (up to 24 h after capsaicin injection). This difference provides the first line of evidence that the neural code for the two forms of hyperalgesia differs.

We wondered whether peripheral sensitization accounts for the secondary hyperalgesia that develops in...
uninjured skin adjacent to an injury. It could be that the sensitization that occurs at the site of injury spreads to adjacent tissue. For example, do the neuropeptides that are released in the area of flare lead to sensitization of the nociceptors? To investigate this, we (and others) applied injuries to part of the receptive area of the nociceptors under study. Sensitization occurs in the injured part of the receptor, but the responses of the uninjured part are not altered (Fig. 7). Thus, sensitization of the peripheral nociceptors does not account for secondary hyperalgesia. Rather, the preponderance of evidence indicates that secondary hyperalgesia is due to changes in the central processing of nociceptive information. We call this “central sensitization.”

One of the most compelling experiments to demonstrate central sensitization is illustrated in Fig. 8. Here, a local anesthetic was injected into the nerve serving the right forearm near the elbow. Capsaicin was then injected into the anesthetized area. There was no pain because the parent nerve was anesthetized, but a flare developed, indicating that the nociceptors had been activated (Fig. 8a). At the same time, the left arm (control) was injected with capsaicin. This produced intense pain, flare, and a large zone of secondary hyperalgesia (Fig. 8b). After the anesthetic had worn off (i.e., 3 h later), the skin was tested again. The left arm still exhibited a large zone of hyperalgesia. In the right arm, the mechanical stimuli felt normal; there was no hyperalgesia.

This experiment demonstrates that anesthetizing the peripheral nerve prevents the development of secondary hyperalgesia. We postulate that the barrage of input from nociceptors at the time of capsaicin injection leads to the development of sensitization in the central nervous system. The anesthetic blocks the signals from the nociceptors from reaching the brain. The nociceptors are still activated since a flare developed, but there is no sensitization in the peripheral tissues.

Figure 7. Tissue injury leads to sensitization of nociceptive fibers at the site of injury, but there is no spread of sensitization to nociceptive terminals outside of the injury site.

Figure 8. A nerve block prevents development of secondary hyperalgesia. (a) A local anesthetic was injected into a nerve near the elbow to produce a large zone of anesthesia in the skin (shaded area). Capsaicin was then injected into the anesthetized area and produced a flare but no pain (left panel). At 3 h later, mechanical testing of the skin revealed no hyperalgesia. (b) Capsaicin was also injected into the opposite arm in the absence of a nerve block and produced a flare and a large zone of hyperalgesia to punctate and stroking stimuli. At 3 h later, the hyperalgesia to punctate stimuli was still present. Solid lines = areas of hyperalgesia to punctate mechanical stimuli; dotted lines = areas of hyperalgesia to light touch; dashed lines = areas of flare. (Used with permission from Ref. 10.)

Signs of central sensitization are already apparent at the spinal cord, where the first synapse in the pain system occurs. Neurons at this level exhibit enhanced responsiveness to mechanical stimuli applied outside the injury area.

**Punctate Hyperalgesia Signaled by A-Fiber Nociceptors**

Before considering which peripheral nerve fibers provide the signal for punctate hyperalgesia, we first
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consider which nerve fibers signal the pain to punctate stimuli in normal skin. We performed psychophysical experiments in which sharp probes of different forces were applied to the back of the hand of normal volunteers. Each probe consisted of a 200-μm-dia. stainless steel wire attached to a rod with a given weight. The weights were varied so that the probes delivered forces ranging from 8 to 512 mN in factor of 2 increments. The probes were applied for 1 s in random order. The subjects reported that these objects produced a sharp pain sensation. They were asked to rate the magnitude of the pain using a 0–100 numerical scale where “0” corresponds to no pain and “100” corresponds to the most intense pain imaginable. The stimulus-response function is shown in Fig. 9a. The threshold for pain was around 16 mN, and the pain ratings increased monotonically with increasing force.

In the same subjects, a fixed pressure was applied to the nerve that supplies the top of the hand. After approximately 45 min, this pressure resulted in a selective block of conduction in A-fibers, but C-fibers still conducted. (This observation is similar to the phenomenon most readers probably have experienced when they wake up in the middle of the night and can’t feel anything in their hand because they have been sleeping on it.) The punctate stimuli were again applied to the hand. The pressure block resulted in a significant decrease in the pain ratings reported by the subjects (Fig. 9a). The pain threshold increased, and the response to suprathreshold stimuli decreased. Thus, when A-fibers are blocked but C-fibers are still conducting, pain ratings to punctate stimuli go down substantially. These data provide psychophysical evidence that A-fiber nociceptors perform a primary role in signaling the pain to punctate stimuli in normal skin.

How do the A-fiber and C-fiber nociceptors respond to these types of stimuli? A Laboratory-developed mechanical stimulator system (see the boxed insert, “Mechanical Stimulator for Studies of Pain”) was employed to apply controlled force stimuli to the skin area where the A-fiber and C-fiber nociceptors terminated. The average response to punctate mechanical stimuli for both nociceptors is shown in Fig. 9b. In these experiments, a 400-μm cylindrical probe was applied to the skin for a period of 3 s, and the stimuli were applied as an ascending series from 40 to 200 mN in 40-mN increments. The response of the A-fiber and C-fiber nociceptors to these forces is considerably different. The response of the A-fibers increases monotonically over this stimulus range, much like the pain ratings did in Fig. 9a. In contrast, the response of the C-fibers reaches a plateau at the higher forces, although pain sensation keeps increasing in that range. These data provide electrophysiological evidence that A-fibers play a major role in signaling the sharp pain to punctate stimuli in normal skin.

Figure 9. A-fiber nociceptors signal sharp pain to punctate stimuli in normal skin. (a) Pain ratings of human subjects to punctate mechanical stimuli. The threshold for pain was around 16 mN, and the pain ratings increased monotonically with increasing force (red curve). When nerve conduction in the A-fibers was blocked, the pain ratings decreased substantially (purple curve). (b) Responses of nociceptors in monkeys to punctate mechanical stimuli. The responses of A-fiber nociceptors increased monotonically with stimulus force. The responses of C-fiber nociceptors reached a plateau at higher stimulus forces.

Punctate Hyperalgesia Signaled by a Subclass of A-Fiber Nociceptors

We now consider whether A- or C-fiber nociceptors signal the enhanced pain to punctate stimuli that develops in the zone of secondary hyperalgesia. To address this question, we made use of another property of capsaicin. Topical application of capsaicin can lead to a desensitization of the skin (desensitization also explains why people who eat hot foods frequently can tolerate higher doses of hot peppers than those who don’t). A 10% capsaicin cream was applied under an occlusive dressing to a small area of the
MECHANICAL STIMULATOR FOR STUDIES OF PAIN

A computer-based electromechanical stimulator system was developed at APL for our neurophysiological and psychophysical studies of pain.\cite{12} The core of the stimulator is a servo-controlled linear motor capable of generating 1 kg of force over a 22-mm range. Three load cells (resolution = 1/8 g, range = 250 g) arranged in an equilateral triangle are attached to one end of the shaft. The interchangeable probe tips are attached at the center of the triangle. Forces collinear and tangential to the probe are calculated using the signal from these three sensors. An optical encoder (resolution = 1 \mu m, range = 25 mm) is positioned on the other end of the shaft and used to measure probe position. A microprocessor-based digital control system permits smooth switching of feedback control between force or position at the 1-kHz update rate.

The stimulator is mounted on a microprocessor-controlled three-axis translation system. This system is used to automatically move the probe to specific locations on the skin over a range of greater than 15 cm to an accuracy of better than 10 \mu m. The stimulator can be programmed to move in a coordinate system parallel to the skin surface being examined.

Photograph of the mechanical stimulator. (Reprinted from Ref. 12 with permission, \copyright 1995, Elsevier.)

In another study using capsaicin to desensitize an area on the forearm,\cite{15} injection of capsaicin between the capsaicin pretreatment area and the vehicle pretreatment area again led to a large zone of secondary hyperalgesia that encompassed the capsaicin pretreatment area. In this study, we obtained pain ratings in response to the application of a blade-shaped probe to the skin with our mechanical stimulator system. Pain ratings increased dramatically after injection of the capsaicin, indicating the presence of mechanical hyperalgesia. The pain ratings at the capsaicin pretreatment area were not significantly different from those at the vehicle pretreatment area (Figs. 10c and 10d). Based on these results, we conclude that hyperalgesia persists in capsaicin-treated areas and that mechano-heat-sensitive nociceptors do not signal punctate hyperalgesia.

In subsequent experiments, we applied a pressure block to the nerve to obstruct A-fiber conduction. We found that hyperalgesia to punctate stimuli disappeared when A-fiber conduction was blocked, but C-fibers were still conducting.\cite{16} We conclude from these experiments that A-fiber nociceptors do not signal punctate hyperalgesia. These A-fibers must be a subset of the A-fiber nociceptors that are neither capsaicin-sensitive nor heat sensitive. Electrophysiological experiments are under way to characterize the properties of these fibers.
NEURAL MECHANISMS OF HYPERALGESIA

Enhanced pain or hyperalgesia occurs after injury to the skin. Primary hyperalgesia develops at the site of injury and is characterized by enhanced pain to mechanical and heat stimuli. Secondary hyperalgesia occurs in uninjured skin surrounding the site of injury and is characterized by enhanced pain to mechanical, but not heat, stimuli. The neural mechanisms of primary and secondary hyperalgesia differ.

An injury (e.g., a burn) to a nociceptor leads to an enhanced responsiveness of the nociceptor called sensitization. This sensitization occurs only for those parts of the nociceptor that are directly injured. Thus, sensitization of nociceptors is thought to account for primary hyperalgesia. Nociceptors in the area of secondary hyperalgesia are not sensitized. Secondary hyperalgesia is thought to be a result of sensitization in the central nervous system.

Hyperalgesia is prevalent in many disease states. The hyperalgesia that occurs in inflammation (e.g., rheumatoid arthritis) is comparable to primary hyperalgesia and is thought to result from nociceptor sensitization. The hyperalgesia to light touch that occurs in neuropathic pain (e.g., shingles) is comparable to secondary hyperalgesia and is thought to be the result of central sensitization.

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CONCLUSIONS

Nerve fiber terminals in the skin that respond selectively to noxious stimuli are called nociceptors. Nociceptors are thought to be responsible for signaling pain sensation. Two classes of nociceptors can be identified based on the speed of action potential propagation in the parent nerve fiber: A-fiber nociceptors (fast) and C-fiber nociceptors (slow). A-fiber nociceptors are responsible for sharp pain sensation in response to punctate mechanical stimuli. C-fiber nociceptors are responsible for the burning pain sensation from hot stimuli.

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