

PERIPHERAL NEURAL CODING OF PAIN SENSATION

The mechanisms by which the sensation of pain is coded in the peripheral nervous system are reviewed. Activity in a specific group of nerve fibers signals the intensity of pain. The increase in pain sensitivity following a burn to the skin is signaled by the increased responsiveness of a subset of these nerve fibers.

INTRODUCTION

When your finger touches a very hot object, you perceive pain as well as other sensations. But how does this happen? The purpose of our research is to understand the physiological basis for the sensation of pain.

Physical stimuli constantly bombard our sensory processes, yet we are able to distinguish the occurrence, location, intensity, and time course of different stimuli. In addition, we are able to perceive different qualities of sensations, such as warmth, cold, touch, and pain. The neurological mechanisms underlying these different cutaneous* sensations are similar. Receptors, which are located near the skin surface, transduce the stimulus energy (for example, heat) into electrical impulses called action potentials. These action potentials travel along the peripheral nerve fibers to the spinal cord and then up to the brain. All action potentials have essentially the same signal strength and are therefore "all-or-nothing" events. The different cells of the nervous system share this common mode of communication, which is analogous to the binary signals in computers.

One of the first issues to consider is whether the signals for the different sensations are multiplexed onto a single line (nerve fiber) or whether each sensation has a dedicated line. Although at one time controversial, the hypothesis that each sensation is subserved by specific receptors that are attached to dedicated lines is supported by recent literature. For example, "touch" receptors have been described that are exquisitely sensitive to light tactile stimuli yet insensitive to heat, whereas "warm" receptors are sensitive to slight changes in temperature but are insensitive to mechanical pressure. Thus, the quality of a sensation depends on which receptors are activated.

Much of the evidence for specificity has been based on sensations other than pain. In fact, many investigators in the past believed that pain was an exception to the rule and that it resulted from overstimulation of receptors that normally subserved other sensations. However, there is evidence to support the idea that receptors exist that are specific for pain sen-

sation. The threshold for activation of these receptors is near the threshold for pain, and their rate of firing increases monotonically with increasing noxious stimulation. In addition, fibers that signal information about noxious stimuli are segregated in the central nervous system from those that signal information about nonnoxious stimuli.

The intensity of a stimulus cannot be coded by the strength of the action potential because all action potentials have the same amplitude. Stimulus intensity can be coded by one or more of the following: (a) the rate of firing of the action-potential impulses, (b) the number of receptors with various thresholds that are activated, or (c) the pattern of signals in different fibers.

Our research on the neurophysiological mechanisms of pain is based on a correlation of the neural responses of single nerve fibers in monkeys with the subjective reports of human subjects exposed to identical stimuli. We have concentrated initially on the peripheral (outside the central nervous system of spinal cord and brain) neural coding mechanism of pain sensation. An understanding of this first level of neural coding will enable us to proceed to study the spinal cord and, eventually, the brain.

LASER THERMAL STIMULATOR

Although cutaneous pain can be elicited by a number of different types of stimuli (for example, pinch, pin prick, extreme cold, chemicals), heat stimuli reliably produce pain and may do this without irreversibly injuring the skin. In 1952, Hardy *et al.*¹ determined that the threshold for thermally induced pain sensation correlated well with skin temperature but not with rate of heat transfer. Since then, many investigators have used constant-temperature stimulators that are based on either resistive heating of a circulating fluid or Peltier heating. The major disadvantages of these contact stimulators are their slow rise times (longer than 1 second for a 10°C step) and the need to touch the skin, which results in an unwanted activation of "touch" receptors.

In order to eliminate contact with the skin, we have developed a noncontact, radiant-heat stimulator that

* See GLOSSARY, page 166.

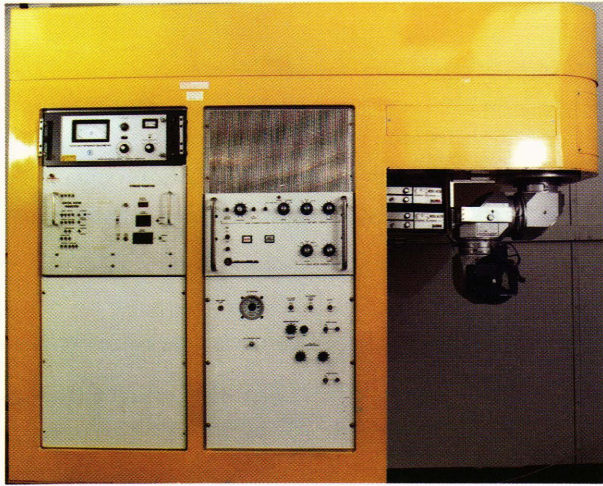


Fig. 1—This laser thermal stimulator provides precise, constant-temperature stimuli on the skin surface for human and monkey experiments. A radiometer remotely measures the skin temperature and controls an infrared laser that heats the skin.

delivers constant-temperature stimuli. The laser thermal stimulator, developed at APL,² is shown in Fig. 1. A carbon dioxide infrared laser used as the heat source is controlled by a radiometer that remotely senses skin temperature. A visible helium-neon laser provides an image of the illuminated area on the skin. Using this device, we achieve step increases in skin temperature with rise rates as fast as 70°C per second and with an accuracy of $\pm 0.1^\circ\text{C}$.

A constant-force mechanical stimulator, also developed at APL,³ is sometimes used to determine the response of different receptors to controlled mechanical stimuli.

PAIN SENSATION IN NORMAL SKIN

Let us first consider pain sensations in the normal skin of human subjects. The skin temperature at which cutaneous pain is first felt is approximately 45°C (113°F). This threshold for thermally induced pain can vary as much as $\pm 5^\circ\text{C}$ for different individuals and for different areas of the body. The pain threshold is influenced by the physical properties of the skin (for example, thickness of calluses) as well as the stimulus history (intensity and duration of previous stimuli and the interval of time between stimuli). Above pain threshold, human ratings of pain increase monotonically with stimulus temperature.⁴ As with pain threshold, ratings of pain to suprathreshold stimuli are also influenced by the stimulus history. For example, when two 45°C, 3-second stimuli are presented, the second stimulus is usually less painful than the first for short intrastimulus intervals (less than 60 seconds), with full recovery occurring after more than 10 minutes.

Two different qualities of sensation are commonly associated with cutaneous pain — a sharp, pricking pain (for example, evoked by a needle jab) and burning pain. Both qualities of pain can be felt for intense

heat stimuli applied to hairy skin. The sharp, pricking sensation is first felt, followed after a brief pause by the burning sensation. On glabrous skin (nonhairy skin, such as the palm), only the second burning sensation is felt for stimulus temperatures below 53°C. The time between the onset of the thermal stimulus and the pricking “first pain” sensation is so short (less than 400 milliseconds for stimuli at the wrist) that fibers having conduction velocities greater than 6 meters per second (A-fibers) must be involved, whereas the burning “second pain” sensation could be mediated by the more slowly conducting C-fibers. For the sake of simplicity, we will describe our results for glabrous skin and not discuss further the neural mechanisms of the first pain sensation felt on hairy skin.

Let us now consider those nerve fibers that are responsive to heat stimuli and, therefore, could code for pain. One group of C-fibers responds to gentle warming of the skin but not to mechanical pressure; they are called “warm” fibers. The response of a typical warm fiber to 3-second stimuli ranging from 41 to 49°C in 2°C increments is shown in Fig. 2. Each stimulus temperature was presented five times and was preceded once by every stimulus. Within these constraints, the order of presentation was randomized. An additional five stimuli at 45°C were presented at the start of each run. This fiber responds to nonnoxious stimuli (for example, 41°C in Fig. 2) and even responds during the 38°C base temperature between stimuli (as is evident by the spike activity preceding the stimuli in Fig. 2). In addition, the response does not monotonically increase with temperature above 47°C. Thus, these warm fibers appear to code for warmth sensation but do not code for pain.

Several investigators have described the response properties of another group of C-fiber afferents that appear to code for pain in uninjured skin.^{4,6} These C-fiber afferents are sensitive to both noxious mechanical and noxious heat stimuli and are referred to as CMH's. The response of a typical CMH to random presentations of 3-second stimuli ranging from 41 to 49°C is shown in Fig. 3. The threshold for response is around 43°C, and the response increases monotonically with temperature above this threshold temperature.

The region on the skin over which these C-fibers are sensitive (the receptive field) is typically circular or elliptical with a mean area of 18.9 ± 3.2 square millimeters. Adjacent CMH's may have overlapping receptive fields. The mean conduction velocity of the CMH's is 0.8 ± 0.1 meter per second.

These nociceptive fibers are readily distinguished from warm fibers by the following characteristics of warm fibers: (a) exquisite sensitivity to gentle warming, (b) failure to respond to mechanical stimuli, and (c) spontaneous activity that stops with cooling of the receptive field. Nociceptive fibers are readily differentiated from touch fibers by the following criteria: (a) touch fibers respond vigorously to application of

Text continued on page 168.

GLOSSARY

AMH — A-fibers sensitive to both mechanical and heat stimuli.

A-fibers — Myelinated nerve fibers having conduction velocities of 3 to 120 meters per second.

Action potential — The all-or-none electrical response of single nerve cells.

Afferents — Nerve fibers that carry signals toward the brain.

CMH — C-fibers sensitive to both mechanical and heat stimuli.

C-fibers — Unmyelinated nerve fibers having conduction velocities of 0.5 to 2.5 meters per second.

Conduction velocity — Speed at which neural signals travel along nerve fibers.

Cutaneous — Relating to the skin.

Glabrous skin — Areas of the body where hair does not normally grow, e.g., palm.

Hyperalgesia — Extreme sensitiveness to painful stimuli.

Myelin — Insulating layer that is wrapped around some nerve fibers.

Nociceptive — Capable of transmitting pain.

Noxious — Injurious, capable of producing pain.

Receptive field — Area on the skin over which a receptor is activated.

Receptors — Endings of nerve fibers that convert an external stimulus into action-potential activity.

EXPERIMENTAL TECHNIQUES

Neurophysiological Experimentation in the Monkey

Animal Model—Ideally, one would like to perform both the neurophysiological and psychophysical experiments on human subjects. Since this is not feasible, our research is based on correlating the physiological response of nociceptive (capable of transmitting pain) fibers in the monkey with the subjective response of human subjects. The selection of monkeys as the best model of human neurophysiology is based on (a) the similarities in structure and density of receptor endings in the two species, (b) the similarities in the sensory pathways in the spinal cords and the brains of the two species, and (c) the demonstration of identical abilities to detect and discriminate mechanical stimuli delivered to the hand. All of the neurophysiological data reported in this paper were obtained from single fiber recordings in the monkey.

Surgical Technique—The monkeys are anesthetized throughout the experiments by intravenous administration of sodium pentobarbital. In addition, body temperature is measured by a rectal probe and maintained at $38.5 \pm 1^\circ\text{C}$ with the use of a heating pad and lamp.

Peripheral nerves with receptors located on the hand are dissected from connective tissue in the upper arm of the monkey. The edges of the incision are sutured to a metal ring to

form a well, and paraffin oil is placed in the well to insulate the nerve electrically from the adjacent tissue and to keep the tissue and nerve from becoming dry.

Under an operating microscope, the outer connective sheaths surrounding the nerve are opened for a distance of 1 centimeter in the direction along the axis of the nerve to reveal the nerve fibers. A small portion of the nerve fibers is cut from the nerve at the end of the opening that is farthest away from the hand. Microsurgical forceps are used to separate this nerve bundle into fine strands suitable for recording from single nerve fibers. The strands typically consist of 5 to 15 active nerve fibers. The dissected nerve filament is wrapped around a 27-gauge platinum wire electrode for unipolar recording. The indifferent electrode is attached to adjacent tissue, and neural recording is begun.

At the end of each experiment, which typically lasts about 17 hours, the wound is flushed repeatedly with saline solution and then sutured. It is possible to use each monkey a number of times, although a different nerve is dissected each time. Because only a small portion of the nerve is actually cut, neurological deficit resulting from these procedures is minimal.

Neural Recording Technique—The block diagram shows the neurophysiological experimental apparatus. The microvolt action-potential

signals are amplified by a low-noise preamplifier made by the Princeton Applied Research Corporation, with a variable gain and a passband from 3 hertz to 10 kilohertz. The output of the amplifier is filtered by a 60-hertz notch filter to minimize "line" noise and is then filtered by a Kronhite variable bandpass filter to optimize the signal-to-noise ratio for a given action potential. A differential amplitude and time discriminator is used to separate the desired impulses from impulses from other fibers and from background noise by providing an adjustable voltage window and time window to screen out irrelevant signals. The action-potential signal is displayed visually on an oscilloscope (along with the time and voltage windows) and acoustically via a speaker. The discriminator provides a digital pulse to the computer for every neural signal that falls within both the amplitude and time windows. The complete experiment is under the control of a PDP-11/34 computer, which turns on the laser stimulator at prescribed intervals and monitors the applied stimulus. It displays on a video terminal the total neural impulse counts for designated time intervals during the experiment (for example, for the interval during which the stimulus is on) and stores the time intervals between neural spikes, as well as other pertinent data, on a floppy disk. In addition, the computer is used off-line to generate replicas of the time course of action

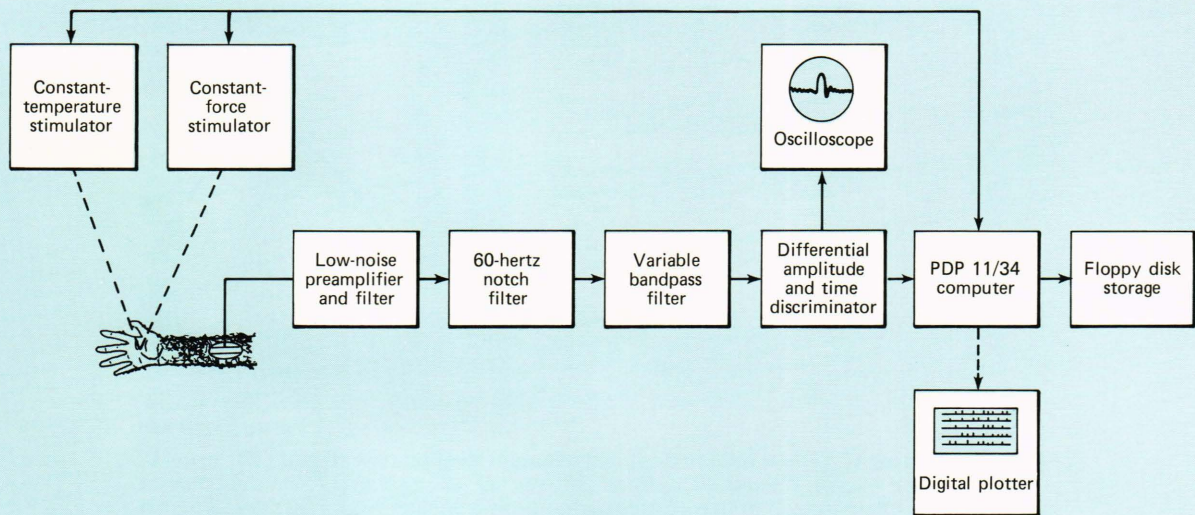


Diagram of neurophysiological experiment. Electrical activity in the peripheral nerve fibers is first amplified and filtered. Activity from a single nerve fiber is selectively gated by means of a variable amplitude and time window discriminator. The computer controls the entire experiment from the timing of the stimuli to the recording of the neural events. The computer is also used off-line for data analysis and plotting.

potentials as well as appropriate histograms, which are plotted on a digital plotter.

Identification of Nociceptive Afferents—Only a fraction of the nerve fibers respond selectively to noxious cutaneous stimuli. Therefore, for each nerve filament that is placed on the recording electrode, we must identify the type of receptors responsible for any spontaneous action-potential activity and then search the surface of the hand for receptors responding exclusively to noxious stimuli. Because most nociceptive afferents appear to respond to strong mechanical pressure (but not to lesser tactile stimuli), we identify nociceptive afferents by firmly squeezing the skin with two fingers. The receptive field (that is, the region on the skin surface over which the receptor is sensitive) is then mapped on the skin with dye at spots where the fiber responds to a small (about 1 millimeter diameter) blunt mechanical probe.

Conduction Velocity Measurement—The speed at which action potentials travel along a nerve is called the conduction velocity. The conduction velocity of a given fiber is a

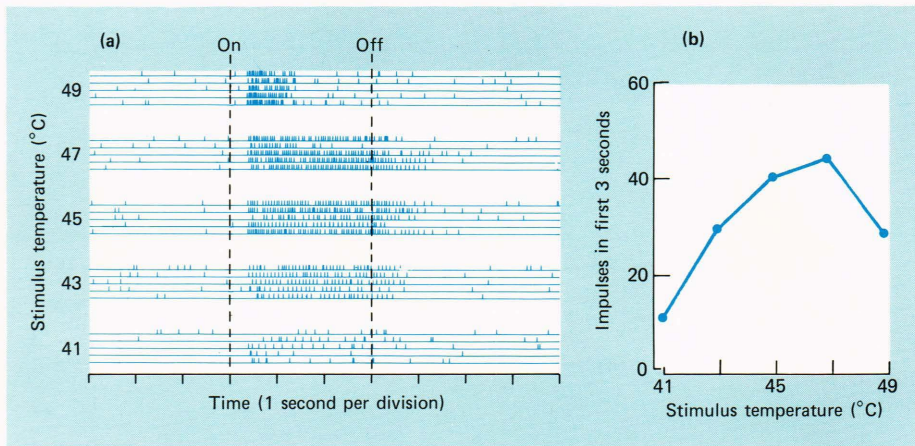
function of the diameter of the fiber (range: 0.3 to 22 micrometers) and depends on whether the fiber is wrapped with an insulating layer of myelin. Unmyelinated fibers have conduction velocities ranging from 0.5 to 2.5 meters per second and are called C-fibers; myelinated fibers have conduction velocities ranging from 3 to 120 meters per second and are called A-fibers. Because nerve fibers are often categorized in these terms, the conduction velocity of each fiber studied is determined at the end of the recording session. The nerve fiber is stimulated by electric shocks delivered through needles placed adjacent to the receptor. The time delay between the electric shock and the arrival of the action potential at the recording electrode, and the distance from the receptor to the recording electrode, are used to estimate the conduction velocity.

Psychophysical Experimentation in Man

In order to understand neural coding mechanisms for pain sensation, it is necessary to measure the

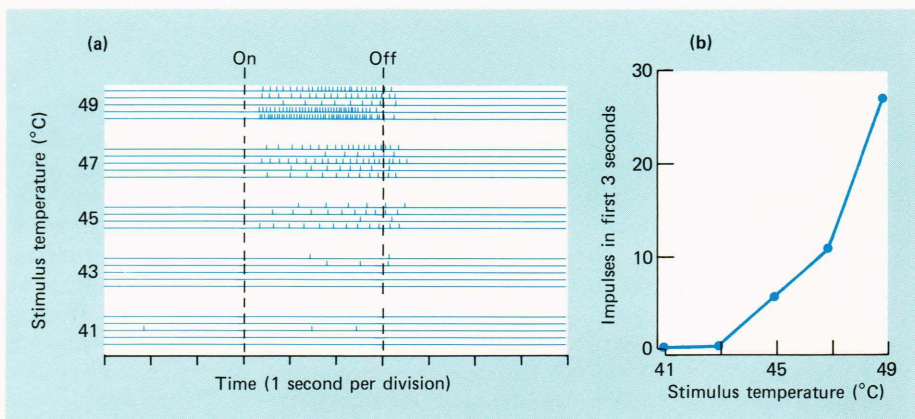
sensation itself in humans. Various scales may be used. The most basic is the “nominal” scale, in which sensations are simply categorized (for example, touch, warmth) and not rank ordered with respect to one another. Another is the “ordinal” scale, in which the responses to different stimuli are rank ordered but their relative magnitude is not specified. The method we have used extensively is called “magnitude estimation.”* This technique allows a ratio scale to be constructed. Here, the ratio of the magnitude of different sensations is specified. If stimulus “x” is rated as 50, and stimulus “y” evokes twice as strong a sensation, then the subject assigns the number 100 to stimulus “y.” Ratio scales are especially valuable in correlational work with neurophysiological studies because the ratio of neural responses can be compared with that of psychophysical responses.

*S. S. Stevens and D. Galanter, “Ratio Scales and Category Scales for a Dozen Perceptual Continua,” *J. Exp. Psych.* 54, 377-411 (1957).



© 1978 *Am. Physiol. Soc.*

Fig. 2—Responses of a warm fiber to 3-second constant-temperature stimuli of 41 to 49°C. (a) Reproduction of neural spike data. Each vertical tick corresponds to one impulse of neural activity; each horizontal line corresponds to one stimulus trial. Trials are grouped according to stimulus temperature. Stimuli were presented in random order at 25-second intervals. Skin temperature was maintained at 38°C between trials. (b) Stimulus-response function for this warm fiber. The average number of impulses during the 3-second stimulus interval is plotted as a function of stimulus temperature. Warm fibers become active for gently warming stimuli and reach a maximum response near pain threshold. Warm fibers do not appear to signal for pain. (From Ref. 4.)



© 1978 *Am. Physiol. Soc.*

Fig. 3—Responses of a nociceptive C-fiber (CMH) whose receptor is located on the palm, to 3-second constant-temperature stimuli of 41 to 49°C. The same format as described in Fig. 2 is used. The threshold for activity in the CMH's is near the pain threshold for uninjured skin in humans, and the responses of CMH's increase monotonically with skin temperature. Therefore, CMH's appear to signal for pain in uninjured glabrous skin. (From Ref. 4.)

blunt objects to the receptive field (this never happens in the case of nociceptive fibers), (b) nociceptive fibers respond most vigorously to stimulation of the receptive field with sharp objects and pinching, and (c) touch fibers do not respond to heat stimuli. “Cold” fibers are distinguished from the other fibers by virtue of (a) their spontaneous activity, (b) the abrupt cessation of spontaneous activity when gentle warming stimuli are applied to their receptive fields, (c) their failure to respond to mechanical stimuli, and (d) their vigorous response to cooling.

In Fig. 4, the mean normalized responses of 15 CMH's are compared with the mean normalized pain ratings of 12 human subjects exposed to identical stimuli. The thermal test sequence consisted of 10

stimuli, each 3 seconds in duration. The first stimulus was always 45°C; the remaining nine stimuli ranged from 41 to 49°C in 1°C increments and were presented in random order. In order to compare the responses of the CMH's and the human subjects, the data were normalized by dividing the response to a given stimulus by the response to the first 45°C stimulus. The close match between the curves in Fig. 4 provides evidence that CMH's code for pain in uninjured glabrous skin.

PAIN SENSATION IN INJURED SKIN

Anyone who has burned himself on a stove knows that injury to the skin often leads to an alteration in

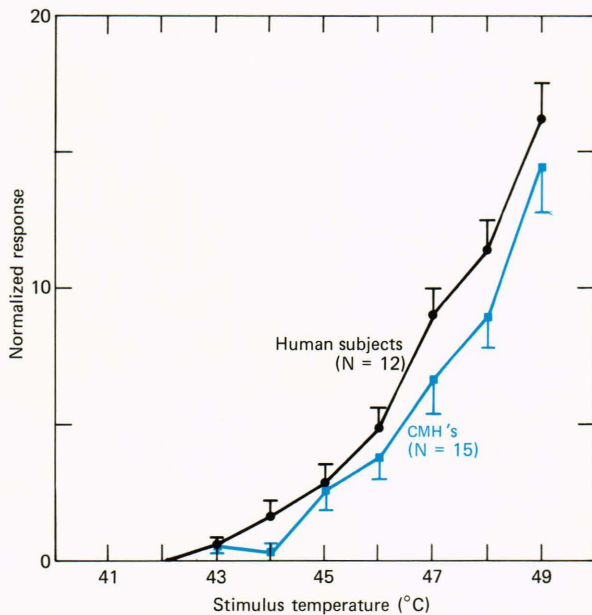


Fig. 4—Normalized response of human subjects and CMH's exposed to identical stimuli. Ten stimuli ranging from 41 to 49°C in 1°C increments were presented in random order every 30 seconds. The response to a given stimulus was normalized by dividing that response by the response to the first stimulus, which was always 45°C. The close match between the curves further supports a role for CMH's in pain sensation.

the pain sensibility at the site of the injury. This increase in pain sensibility is termed hyperalgesia and is characterized by spontaneous pain and a decrease in pain threshold. Stimuli that before the burn were not painful (for example, gentle warming or light touching) can be quite painful after the burn. Hyperalgesia is believed to be the result of an increased responsiveness (called sensitization) of the receptors of the nociceptive afferents.

To determine the role of CMH's in hyperalgesia, we compared the responses of CMH's and the ratings of pain by human subjects before and after a 53°C, 30-second burn to the hand. After this burn, the skin of human subjects became hyperalgesic within minutes. Pain was present even without stimulation. As shown in Fig. 5a, the threshold for pain decreased significantly; the 41°C stimulus, which before the injury was not painful, was more painful after the injury than the 49°C stimulus before the injury. In addition, the magnitude of pain increased significantly for stimuli that were originally slightly painful. For example, the mean rating for the 49°C stimulus after the injury was four times the rating of the same stimulus before the burn.

The mean responses of the CMH's before and after the 53°C, 30-second burn are shown in Fig. 5b. The activity in CMH's was suppressed, not sensitized, after the burn; the response to the more intense stimuli decreased. In addition, the threshold for neural activity increased. Therefore, the hyperalgesia that is

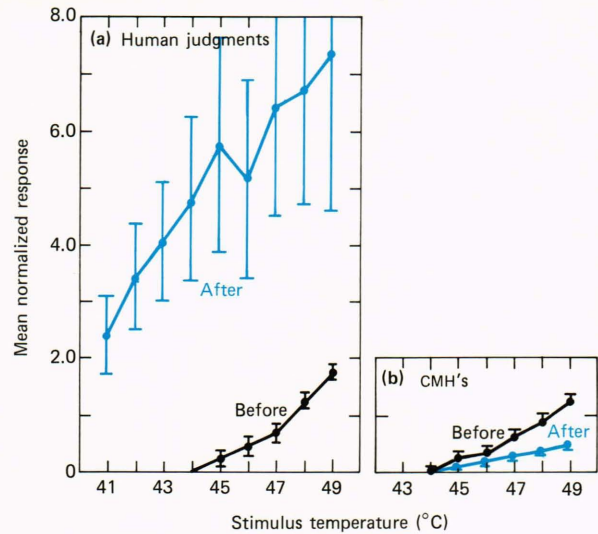


Fig. 5—Mean normalized response of human subjects and CMH's before and after a 53°C, 30-second burn to the glabrous hand. (a) Pain ratings by human subjects increased dramatically 10 minutes after the burn. (b) The response of the CMH's decreased after the burn. The CMH's do not appear to signal the increased pain sensitivity that occurs in humans after a burn to the glabrous hand. (From Ref. 7. Copyright 1981 by the American Association for the Advancement of Science.)

experienced by human subjects after a burn cannot be explained by the activity of CMH's.

We have recently discovered a new group of nociceptive afferents that might account for this hyperalgesia.⁸ These fibers have a mean conduction velocity of 31.1 ± 1.5 meters per second and, therefore, would be classified as A-fibers. They are responsive to intense mechanical and intense heat stimuli and, therefore, are called AMH's. The response of a typical AMH to repeated presentations of a 53°C, 3-second stimulus is shown in Fig. 6. The fiber did not respond to the initial presentation of the 53°C stimulus, but thereafter developed a pronounced response that reached a plateau after about 25 trials. This sensitization after exposure to intense stimuli was typical of the AMH's.

The heat thresholds of the AMH's decreased significantly after exposure to intense heat stimuli (for example, repeated presentations of 53°C, 3-second stimuli). As shown in Fig. 7, the AMH's were relatively insensitive to heat before sensitization. In fact, the majority (25 of 42) failed to respond initially to stimuli of less than 53°C. In contrast, the mean heat threshold for CMH's was 43.6 ± 0.6 °C.⁴ After the intense heat stimuli, the heat thresholds for a majority of the AMH's were lower than 45°C, whereas the heat thresholds of CMH's increased after similar stimuli.

The response of AMH's before and after the 53°C, 30-second burn in human subjects is shown in Fig. 8. Before the burn, the AMH's gave a meager response; however, after the burn, the response was greatly enhanced. The threshold for response decreased signifi-

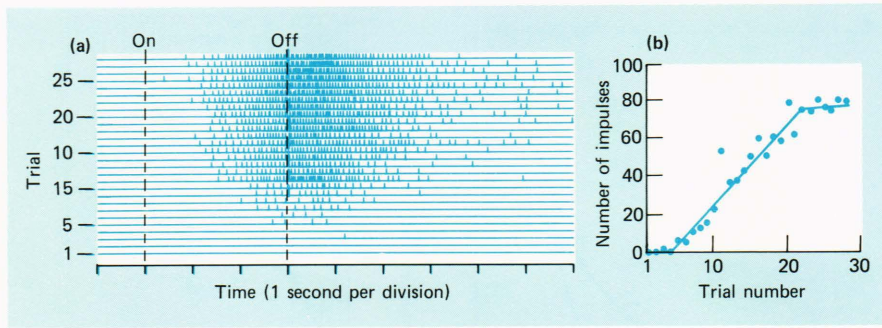


Fig. 6—Response of a nociceptive A-fiber (AMH) to repeated presentations of a 53°C, 3-second stimulus. The response increased with repeated exposures to the stimulus. This sensitization was typical of the AMH's. (a) Reproduction of neural spike data. Each horizontal line corresponds to one trial and trials are arranged in sequence from bottom to top. (b) Sensitization curve. Total responses for each trial are plotted as a function of trial number. The skin temperature between trials was maintained at 38°C. Stimuli were repeated every 28 seconds. (From Ref. 8.)

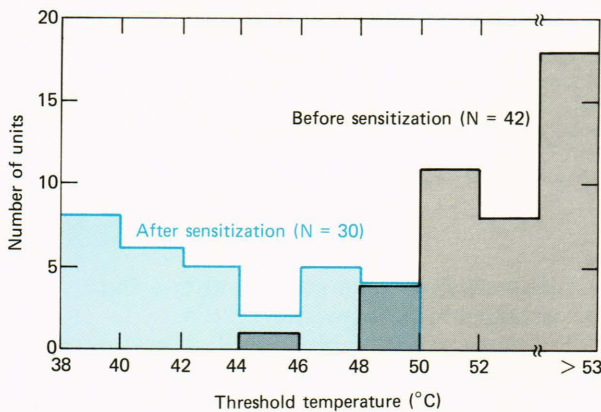


Fig. 7—Thermal thresholds for the AMH's before and after sensitization. The heat thresholds of all AMH's decreased after exposure to intense heat stimuli. The data labeled >53°C correspond to fibers that did not respond to the maximum stimulus in the threshold series. (From Ref. 8.)

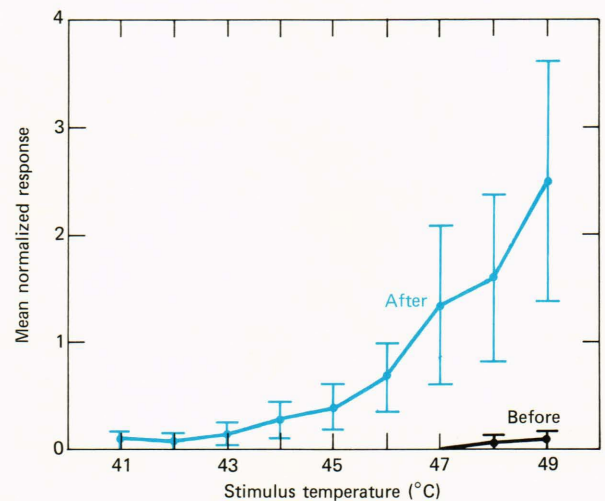


Fig. 8—Mean response of AMH's before and after a 53°C, 30-second burn to the glabrous hand. The response of the AMH's increased significantly 10 minutes after the burn and thus matched the increased pain ratings of human subjects after the burn (see Fig. 6). The AMH's, therefore, appear to signal the increased pain sensitivity (hyperalgesia) following an injury to glabrous skin. (From Ref. 7. Copyright 1981 by the American Association for the Advancement of Science.)

cantly, and the response to the more intense stimuli increased. In addition, some of the AMH's developed spontaneous activity. These signs of sensitization observed in the AMH's are consistent with the signs of hyperalgesia described earlier for the human subjects. Thus, AMH's appear to code for hyperalgesia in man.

The average responses of human subjects, AMH's, and CMH's during the 53°C, 30-second burn are shown in Fig. 9. For the human subjects, the pain remained intense throughout the burn at a level about 10 times that for the 49°C stimulus before the burn. The response of the AMH's increased during the first 5 seconds and remained at a high level for the remainder of the stimulus. The CMH's had a significant initial response that diminished to a relatively low level within 5 seconds. Thus, the AMH's appear to code for the pain during a prolonged, intense stimulus as well as for hyperalgesia.

As an additional test of the role of AMH's and CMH's in pain sensation, a separate experiment was

performed on two subjects. Twenty minutes after the 53°C, 30-second burn, a blood pressure cuff was placed on the upper arm and inflated to a pressure of 250 mmHg (33 kilopascals) — sufficient to stop blood flow in the arm. This resulted in a gradual block of action-potential conduction in the nerve fibers, with the A-fibers blocking before the C-fibers. After 40 minutes, light-touch and cold sensitivity and motor function were gone, indicating that conduction in the A-fibers was at least partially blocked. At this time, a thermal test sequence at the site of the burn indicated that the hyperalgesia was markedly decreased. The pain evoked by a thermal test sequence at nearby uninjured skin was not reduced.

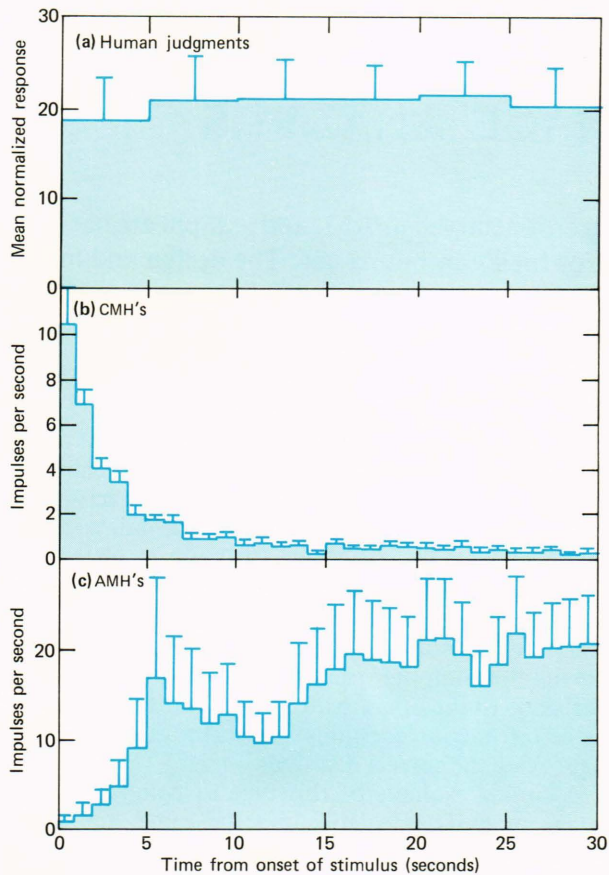


Fig. 9—Response of (a) human subjects, (b) CMH's, and (c) AMH's during the 53°C, 30-second burn. The pain remained intense throughout the burn for the human subjects. The response of the CMH's decreased significantly during the first 5 seconds of the burn and remained at a relatively low level. In contrast, the response of the AMH's increased during the first 5 seconds and remained at a relatively high level. The AMH's, therefore, appear to signal for the pain during a prolonged, intense stimulus. (From Ref. 7. Copyright 1981 by the American Association for the Advancement of Science.)

These data support the view that hyperalgesia is signaled by A-fibers. In addition, because the pain in uninjured skin did not decrease, the data also support the view that pain in uninjured skin is signaled by C-fibers.

CONCLUSIONS AND FUTURE PLANS

The evidence reported here, as well as other evidence, supports the following conclusions concerning the peripheral neural mechanisms for pain in the glabrous hand. Pain sensation is signaled by activity in dedicated nerve fibers that have receptors specifically sensitive to noxious stimuli. C-fiber nociceptive afferents appear to code for the intensity of thermal pain near pain threshold (43 to 48°C) in the uninjured hand; above 48°C, myelinated nociceptive afferents contribute to pain sensation. These A-fiber

nociceptive afferents appear to code for the pain during intense, prolonged stimuli (for example, 53°C, 30 seconds) and also for the hyperalgesia after a burn to the glabrous hand.

At the present time we do not know what causes the AMH's to become sensitized after a burn. Current evidence suggests that a chemical substance (for example, bradykinin) is released at the site of the burn and produces hyperalgesia in human subjects. Future experiments will be directed toward understanding the biochemical processes underlying the hyperalgesia in humans and sensitization of AMH's.

Although we believe we understand the neural mechanism underlying hyperalgesia for glabrous skin, preliminary experiments on hairy skin gave quite different results. After a 53°C, 30-second burn to the hairy skin of seven human subjects, the threshold for pain decreased but the responses to stimuli above 46°C did not significantly change. Although AMH's innervating hairy skin became sensitized, the relative density of AMH receptors on hairy skin appears to be substantially less than that on glabrous skin. Additionally, many CMH's with receptors on hairy skin showed signs of sensitization. The response properties of the A-fibers responsible for the first pain sensation on hairy skin have not been well documented. In future experiments we hope to determine the relative roles of A- and C-fiber nociceptive afferents in pain sensations of hairy skin.

REFERENCES

- 1 J. D. Hardy, H. G. Wolff, and H. Goodell, *Pain Sensations and Reactions*, Williams & Wilkins, Baltimore (1952).
- 2 R. A. Meyer, R. E. Walker, and V. B. Mountcastle, "A Laser Stimulator for the Study of Cutaneous Thermal and Pain Sensations," *IEEE Trans. Biomed. Eng.* **23**, 54-60 (1976).
- 3 J. G. Chubbuck, "Small-Motion Biological Stimulator," *APL Tech. Dig.* **5**, 18-23 (1966).
- 4 R. H. LaMotte and J. N. Campbell, "Comparison of Responses of Warm and Nociceptive C-Fiber Afferents in Monkey with Human Judgments of Thermal Pain," *J. Neurophysiol.* **41**, 509-528 (1978).
- 5 R. E. Beitel and R. Dubner, "Response of Unmyelinated (C) Polymodal Nociceptors to Thermal Stimuli Applied to Monkey's Face," *J. Neurophysiol.* **39**, 1160-1175 (1976).
- 6 P. Bessou and E. R. Perl, "Response of Cutaneous Sensory Units with Unmyelinated Fibers to Noxious Stimuli," *J. Neurophysiol.* **32**, 1025-1043 (1969).
- 7 R. A. Meyer and J. N. Campbell, "Myelinated Nociceptive Afferents Account for the Hyperalgesia that Follows a Burn Applied to the Hand," *Science* **213**, 1527-1529 (1981).
- 8 J. N. Campbell, R. A. Meyer, and R. H. LaMotte, "Sensitization of Myelinated Nociceptive Afferents that Innervate Monkey Hands," *J. Neurophysiol.* **42**, 1669-1679 (1979).

ACKNOWLEDGMENTS—Dr. Robert LaMotte of Yale University collaborated with us on much of the research reported here. Dr. Vernon Mountcastle provided encouragement and support for this project in the initial phases. Additionally, we greatly appreciate the dedicated assistance of Susan M. Lancelotta and Susan R. Jaffe and the help of Shawn J. Bird, Rodney Willoughby, and JoAnne M. Campitell. We are particularly grateful for the generous support of Edith Rothschild Weinberg and E. David Weinberg, M.D.

This research was supported by U.S. Public Health Service research grant NS-14447 and Teacher-Investigator Award NS-00519 of the National Institute of Neurological and Communicative Disorders and Stroke.