Peripheral Mechanisms of Somatic Pain

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Summary

Pain is the perceptual counterpart of the body's response to stimuli that threaten the integrity of its tissues. The aversive nature of pain strongly motivates the organism to avoid these noxious stimuli. Additionally, pain may help promote healing by motivating the organism to avoid contact or motion of an injured area. However, pain may persist beyond its useful purpose and result in profound behavioral disturbances and suffering.

Recent research has improved our understanding of the neural substrates of pain sensation: 1) mammals have been shown to have specialized peripheral sense organs for detecting noxious stimuli; 2) the information signalled by these receptors is transmitted rostrally by neurons forming a distinct subset of afferent systems projecting to the somatosensory cortex; 3) the central processing of afferent information in the dorsal horn is modulated by activity descending from rostral areas of the central nervous system; and 4) several candidate neurotransmitters have been identified that serve as synaptic links in the dorsal horn for afferent fibers. Some of these neurotransmitters may be specific for signalling pain. In this review, we will focus on peripheral neural events concerned with pain of somatic origin.

Nociceptors

ROLE OF NOCICEPTORS IN SIGNALLING PAIN SENSATION

How the nervous system differentiates between the various forms of sensory experiences has been a controversial issue since the beginning of sensory physiology. The two principal theories which have been proposed are the pattern theory and the specificity theory. According to the pattern theory, the perceived sensation is determined by the pattern of input from the skin. Thus, a particular sensation is not associated with a specific receptor, but, rather, with the spatial and temporal pattern of nerve impulses from multiple receptors. In addition, it is argued that pain, unlike touch, cold, and warmth, is not a primary sensory modality, but, rather, the sensation evoked at the ex-


<table>
<thead>
<tr>
<th>Property</th>
<th>CMHs*</th>
<th>Type I AMHs†††</th>
<th>Type II AMHs‡††</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive field area (mm²)</td>
<td>19 ± 3‡</td>
<td>37 ± 4††</td>
<td>1–4†††</td>
</tr>
<tr>
<td>Skin type</td>
<td>Glabrous and hairy</td>
<td>Glabrous and hairy</td>
<td>Hairy only</td>
</tr>
<tr>
<td>Heat threshold (°C)</td>
<td>43.6 ± 0.6‡‡</td>
<td>&gt;49††</td>
<td>45††</td>
</tr>
<tr>
<td>Receptor utilization time (to heat) (ms)</td>
<td>&gt;50§</td>
<td>Long (&gt;600)§∥∥</td>
<td>Short (&lt;200)‡∥∥</td>
</tr>
<tr>
<td>Heat response characteristic</td>
<td>Slowly or quickly adapting§</td>
<td>slowly adapting‡</td>
<td>quickly adapting‡ ∥∥</td>
</tr>
<tr>
<td>Mechanical threshold (bars)</td>
<td>6.0 ± 0.6‡‡</td>
<td>3.5 ± 0.3†∥∥</td>
<td>1.7 (0.4 gm)†∥∥</td>
</tr>
<tr>
<td>Conduction velocity (m/s)</td>
<td>0.8 ± 0.1‡∥∥</td>
<td>31.1 ± 1.5†∥</td>
<td>15.2 ± 9.9†∥∥</td>
</tr>
<tr>
<td>Presumed physiological role</td>
<td>Burning pain (second pain)</td>
<td>Hyperalgesia after injury to glabrous and possibly hairy skin</td>
<td>Pricking pain (first pain)</td>
</tr>
</tbody>
</table>

* CMHs = C-fiber mechano-heat afferents.
† AMHs = A-fiber mechano-heat afferents.
‡ From reference 124.
§ From reference 161.
¶ From reference 51.
∥ From reference 30.
∥∥ From reference 56.

The table above lists the properties and presumed physiological roles of nociceptive afferents sensitive to mechanical and heat stimuli. The table includes the receptive field area, skin type, heat threshold, receptor utilization time, heat response characteristic, mechanical threshold, conduction velocity, and presumed physiological role. The table compares the properties of CMHs, Type I AMHs, and Type II AMHs.

The extreme of the primary sensation. One variation of the pattern theory is the "gate control theory" initially proposed by Noordenbos and later popularized by Melzack and Wall. According to this theory, pain is related to the balance of input between large and small diameter afferents. As the balance shifts towards more input from small diameter afferents, pain is perceived.

According to the specificity theory, specialized cutaneous receptors and neural pathways exist for each modality of sensation arising from cutaneous stimulation. Thus, cold and warm sensations are signalled by specific classes of A-delta and C-fibers, respectively, while touch sensations are signalled by classes of A-beta fibers. Several lines of evidence indicate a specific role for thinly myelinated and unmyelinated fibers in signalling pain sensations. Congenital neuropathies associated with absence of thinly myelinated and unmyelinated fibers result in insensitivity to pain, while the perception of pain is unimpaired in large fiber neuropathies. Conduction blockade of large myelinated fibers in peripheral nerves by ischemic compression results in selective loss of cutaneous tactile sensation without analgesia. In addition, it has been observed that, during electrical stimulation of a peripheral nerve with concurrent proximal recording of the compound action potential, pain is sensed only when the A-delta and C-fibers are activated. The pioneering work of Zotterman, and more recently, single fiber recordings in experimental animals and microneurographic recordings in humans, have identified a class of cutaneous afferent fibers with receptors that respond preferentially to high intensity stimuli. Much evidence indicates that these receptors, termed nociceptors, encode the occurrence, intensity, duration, and location of noxious stimuli and signal pain sensation. Nociceptors can be classified according to: 1) their response to different modalities of intense stimulation, 2) the conduction velocity of their peripheral axons, and 3) differences in the characteristics of their response to stimuli.

**CLASSIFICATION OF NOCICEPTORS**

Cutaneous Nociceptors. Cutaneous nociceptive afferents may be myelinated (A-fibers) or unmyelinated (C-fibers). Many of the unmyelinated fibers respond to a wide range of noxious stimuli, including noxious mechanical, heat, and chemical stimuli, and are therefore called polymodal nociceptors. Hardy et al. found that heat stimuli can be used to produce pain sensation reliably. They determined that the pain threshold is related to the temperature of the heat stimulus, and not to the rate of heat transfer. Since then, most studies of pain and nociception have focused on the responses to heat stimuli.

C-fibers with receptors that respond to noxious mechanical and heat stimuli, often referred to as C-mechano-heat (CMHs) receptors, are found in the skin of most species. The corresponding A-fiber nociceptive afferents are termed AMHs. A summary of properties of the mechano-heat nociceptive afferents appears in table 1. Some myelinated and unmyelinated afferents have receptors that respond only to intense noxious mechanical stimuli, and have, therefore, been called high threshold mechanoreceptors (HTMs). A small percentage of myelinated and unmyelinated afferents respond to noxious mechanical and cold stimuli, but not to heat. Other nociceptors that respond only to intense cold or intense heat have also been reported. The presence in the human skin of specific chemosensi-
tive nociceptors has also been suggested. Some nociceptors respond only to frankly noxious stimuli. For others, the threshold for a response occurs for stimuli that are neither noxious nor perceived as painful. However, all nociceptors exhibit a monotonically increasing response to stimuli in the noxious range.

**Mechano-heat nociceptors: C-fiber mechano-heat nociceptors (CMHs):** Several lines of evidence indicate that CMHs code for pain from heat stimuli applied to the skin. First, recent studies have used the strategy of comparing the pain ratings of human subjects (using magnitude estimation techniques) with neurophysiological responses of CMHs in anesthetized monkeys exposed to identical heat stimuli. Studies on the glabrous skin of the hand demonstrate a remarkable correlation between human pain ratings and activity of CMHs (fig. 1). Second, the threshold of CMHs recorded in animals is similar to the pain threshold in humans (about 45°C). Third, the response of CMHs to suprathreshold heat stimuli increases monotonically with increasing stimulus intensity (fig. 2). Fourth, both selective A-fiber ischemic blocks and C-fiber (local anesthetic) blocks indicate that C-fiber function is sufficient for thermal pain perception near the pain threshold. And, fifth, repeated stimulation with radiant heat results in suppression of warmth and painful heat sensations. Similar stimulus-interaction effects are observed in recordings from CMHs in monkey.

Microneurography (see Appendix 1) in awake humans has provided additional evidence for the role of CMHs in coding for pain. First, the heat threshold for activating CMHs is usually just below the pain threshold. Second, a linear relationship exists between responses of CMHs and ratings of pain over the temperature range of 39°C to 51°C. Third, stimulus interaction effects, similar to those seen in the animal studies, have been observed with microneurographic recordings in humans. And, fourth, intraneuronal micro-stimulation of presumed single identified CMHs in humans elicits aching or burning pain.

**A-fiber mechano-heat nociceptors (AMHs):** Myelinated nociceptive afferents with conduction velocities in the 5-55 m/s range (A-delta and A-beta range) have been observed in rat, rabbit, cat, and monkey. Thinly myelinated fibers with response characteristics similar to those described in other mammalian species have recently been reported in human skin nerves, as well.

Two distinct classes of AMHs with different heat response characteristics have been observed. These have been called type I and type II AMHs (table 1). Type I AMHs are found in both glabrous and hairy skin, and have a high threshold to heat stimuli—generally greater than 49°C. Type I AMHs have a long receptor utilization time to heat stimuli (time between stimulus onset and initiation of action potential activity), and respond throughout a prolonged stimulus. Type II AMHs are found less frequently than type I AMHs. To date, they have only been seen in hairy skin. They are characterized by sensitivity to heat similar to that of CMHs (threshold near 43°C), short receptor utilization time, and a quickly adapting response to stepped heat stimuli.

A role of type I AMHs is apparent from comparison of human pain ratings with responses of nociceptive afferents during a sustained high-intensity stimulus. A 53°C, 30-s stimulus evokes a sustained high level of pain. When CMHs are exposed to the same stimulus, they respond vigorously only in the first few seconds. In contrast, type I AMHs respond vigorously beginning several seconds into the stimulus. A characteristic feature

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**FIG. 1.** Normalized responses of human subjects and C-fiber mechano-heat nociceptor (CMHs) in monkey exposed to identical heat stimuli on glabrous skin. The close correlation between the curves supports a role of CMHs in pain sensation. The thermal test sequence consisted of a 45°C stimulus followed by a random sequence of nine stimuli ranging from 41°C to 49°C. Human judgments of pain were measured with the magnitude estimation technique: Subjects assigned an arbitrary number (the modulus) to the magnitude of pain evoked by the first 45°C stimulus and judged the painfulness of all subsequent stimuli relative to this modulus. The response to a given stimulus was normalized by dividing by the modulus for each human subject or by the average response to the first 45°C stimulus for the CMHs. From Meyer RA, Campbell N: Peripheral neural coding of pain sensation. Johns Hopkins APL Technical Digest 2:164-171, 1981, with permission.
of type I AMHs is the change in responsiveness produced by repetitive heat stimulation or heat injury to the skin.\textsuperscript{51,69,109,115} This phenomenon, termed sensitization, will be discussed in detail in the following section on Hyperalgesia and Sensitization of Nociceptors.

Noxious heat stimuli applied to the hairy skin of the hand or forearm evoke a double pain sensation perceived as stinging pain followed by burning pain. This is often referred to as first pain and second pain, respectively.\textsuperscript{142,186,204} Latency measurements of the first pain sensation in human subjects indicate that the responsible afferents must have conduction velocities in the A-fiber range.\textsuperscript{28} The response properties (low heat threshold, short utilization time, and burst response to heat) of type II AMHs make them ideal candidates for subserving first-pain sensations.\textsuperscript{30,53,56,114} Second pain sensation is signalled by the slower conducting C-fiber nociceptors.\textsuperscript{184}

**High-threshold mechanoreceptors (HTMs):** These nociceptors respond only to intense mechanical stimuli, but not to heat stimuli. HTMs with myelinated afferents have been described to have large, multi-point receptive fields. While some sensitive HTM units respond to stimuli which are not overly noxious, their thresholds are usually much higher than low-threshold mechanoreceptors, and noxious pressures are required for maximal response.\textsuperscript{24,35,49,76,180} Since the heat threshold of AMHs is generally greater than the maximum heat stimulus used in most studies, many HTMs may actually be AMHs. In humans, recordings have been made from a subgroup of A-delta fibers which respond only to high-threshold mechanical stimulation, and not to heat.\textsuperscript{2} High-threshold mechanoreceptors that do not respond to heat with unmyelinated afferents have also been described in the cat and monkey.\textsuperscript{15,270} In the monkey, they comprise only a small percentage (<10%) of the C-fiber population.\textsuperscript{76}

**Correlation of nociceptor activity and pain sensation:** As we discussed in earlier sections, there is a good correlation between nociceptor discharges to heat stimuli and human pain ratings. However, there are some inconsistencies. For example, the lowest stimulus levels which excite nociceptors are not always perceived as painful by human subjects.\textsuperscript{218} Also, intrafascicular electrical shocks at an intensity adequate to evoke a single spike of a CMH are most often not perceived at all by the subject.\textsuperscript{90}

The correlation between pain thresholds and thresholds for nociceptor activation is less striking for mechanical stimuli than for heat stimuli. Mechanical stimulation at intensities that evoke up to 10 impulses/sec in CMHs is not accompanied by sensation of pain, whereas heat stimulation resulting in responses of 3 impulses/s results in pain.\textsuperscript{221} The mechanical threshold for the nociceptors\textsuperscript{124} is 6.0 ± 0.6 bars for CMHs (mean ± SEM) and 3.5 ± 0.3 bars for type I AMHs,\textsuperscript{31} but the mechanical threshold for pain on glabrous skin in humans is 12.0 ± 1.1 bars (1 bar = 10^5 dynes/cm^2).\textsuperscript{198} During long-lasting noxious mechanical stimulation in human volunteers, the intensity of pain elicited is directly proportional to the intensity of the stimulus, and has a tendency to increase throughout the 120-s stimulus period.\textsuperscript{3} In contrast, discharges of polymodal C-fiber nociceptors in man show an initial high frequency dynamic discharge followed by adaptation. Thus, the time course of the stimulus-induced pain sensations does not
correlate with the activity in C-fiber nociceptors. The above-mentioned discrepancies have led some investigators to suggest that central processes determine threshold, intensity, and modality of sensations, including pain. The central processing may be in the form of spatial or temporal summation of input from primary afferents. One line of evidence for central spatial summation stems from the observations that the pain threshold, during intraneural microstimulation of CMHs, is lower at 10 Hz than at 1 Hz. Thus, at lower frequencies, inputs from several fibers are needed to evoke pain sensation. In addition, evidence for temporal summation stems from the observation that, at a constant stimulation intensity, the time required to reach a certain intensity of pain is dependent on the stimulus frequency; that is, the number of evoked impulses. Evoked pain takes several seconds to build up at lower (1–5 Hz) stimulation frequencies, while, at 10 Hz, pain magnitude peaks rapidly, though the same number of axons are presumably excited. It is likely that spatial and temporal summation of nociceptor impulses at central levels are needed to evoke pain under most circumstances. Thus, a punctuate mechanical stimulus which results in a relatively vigorous response in a few nociceptors is not perceived as painful, whereas a large heat stimulus which evokes a weak response in a large number of receptors results in pain sensation. Another possibility is that mechanical stimulation also activates low threshold mechanoreceptors, which have an inhibitory influence in the central nervous system on the input via nociceptive afferents. This second hypothesis is supported by the observation that pain induced by intraneurical electrical stimulation at C-fiber strength can be substantially reduced by vibration of the skin within the projected pain region. The central nervous system, therefore, has an important modulatory role in inhibiting or summing the information it receives from the peripheral nociceptors.

Muscle Nociceptors. Candidate nociceptor afferents in muscles include small myelinated (group III) and unmyelinated (group IV) afferent fibers. Presumably, the receptors for the muscle nociceptor afferents are the many free nerve endings found in the connective tissue of the muscle, between muscle fibers, in blood vessel walls, or in tendons. These form as much as 75% of the sensory innervation of skeletal muscle, and are thought to signal the pain experienced during muscular cramps or after strenuous exercise.

Myelinated (group III) muscle afferents: The group III thinly myelinated afferents (conduction velocity 2.5–20 m/s) are usually excited by mechanical stimuli applied either to the muscle or its tendon, and generally do not respond to stretch or contraction. These afferents have been termed “pressure-pain” fibers, because of the possibility that they may have some role in pain originating in muscle. The majority (56%) of the fine myelinated group III afferents have high thresholds for mechanical stimulation and require noxious pressure for excitation. Some of the afferents (35%), however, respond to light pressure, while a small proportion (9%) of afferents are not excited by mechanical stimulation.

Several types of pressure receptors have been recognized. One kind is activated chiefly by pressure on the musculo-tendinous junction, and responds with a slowly adapting discharge. Others with large receptive fields are activated by compression of the muscle belly. Some fibers have a rapidly adapting discharge, and are excited by pressure applied to a localized region within a muscle.

Most of the myelinated afferents (71%) can also be excited by intra-arterial injections of algesic substances, such as bradykinin, serotonin, potassium chloride, and 6% sodium chloride. Responsiveness to algesic substances is not restricted to the putative me- chanosensitive fibers with high thresholds, but also extends to low threshold pressure sensitive units. About half of the high threshold units and two-thirds of the afferents with low mechanical thresholds respond to both noxious mechanical and chemical stimuli. In addition, some of these muscle afferents respond to thermal stimuli applied to the muscle belly, and thus behave as polymodal nociceptors.

Unmyelinated (group IV) muscle afferents: The group IV unmyelinated afferents (conduction velocity <2.5 m/s) have response properties similar to the myelinated nociceptive afferents, except that their thresholds to mechanical stimuli tend to be higher. The majority (64%) of these afferents respond only to strong pressure. A small fraction (4%) respond to light pressure, and about one-third cannot be excited by local mechanical stimulation. About half of the unmyelinated afferents are readily activated by algesic chemicals, such as bradykinin, serotonin, histamine, and potassium ions. Prostaglandin (PG E2) and serotonin have been found to enhance the sensitivity of the group IV muscle afferents to intra-arterial doses of bradykinin. The proportion of afferents with high and low mechanical thresholds responding to chemical stimuli is similar to that of the myelinated afferents. Most of the afferents are also responsive to thermal stimulation. Many of these fibers thus behave like C-polymodal nociceptors innervating the skin.

Role of muscle nociceptors in pain: Muscle pain is a fre-
Responses to movements

A

Group II

33% 56%

Group III

24% 33.5%

Group IV

36.5% 19.5%

B

Inflammation

3% 5%

7%

89%

14%

72%

- activated by nonnoxious movements (category 1)
- weakly activated by nonnoxious movements (category 2)
- activated only by noxious movements (category 3)
- not activated by movements (category 4)

Fig. 3. Comparison of the responses of group II (c.v. 20-40 m/s), group III (c.v. 25-20 m/s), and group IV (c.v. <2.5 m/s) afferents from the cat's normal (A) and inflamed (B) knee joint to passive movements. Note the increased incidence of afferents in both groups III and IV that respond to nonnoxious movements in the inflamed joints. (From Heppenmann B, Herbert MK, Schäuble HG, Schmidt RF: Morphological and physiological characteristics of the innervation of cat normal and arthritic knee joint. *Effects of Injury to the Trigeminal and Spinal Somatosensory System*. Edited by Pulols LS, Sesse BJ. New York, Alan R. Liss, 1987, pp 19-27, with permission.)

Contractions of muscle while the arterial circulation is occluded.\textsuperscript{149} In addition, acetylcholine acid reduces the excitation of these muscle afferents by algesic agents, such as bradykinin.\textsuperscript{152} It has, therefore, been suggested that these fibers might contribute to ischemic muscle pain. The differential role, if any, of the myelinated and unmyelinated muscle nociceptors is unclear at the present time.

Joint Nociceptors. Nerve fiber counts in the articular nerves of cats reveal that the predominant population of joint afferents is formed, not by large afferents, but, rather, by small myelinated A-delta (group III, conduction velocity 2.5-20 m/s) and unmyelinated C-fiber afferents (group IV, conduction velocity <2.5 m/s).

Recordings have been made from A-delta and C-fiber joint afferents of the cat knee, both in normal animals and in animals with acute experimentally induced arthrosis.\textsuperscript{40,95} The receptive fields of these afferents from normal joints are often limited to one to four small, discrete spots. The mechanical thresholds of A-delta (group III) afferents are on average lower than the C-fiber (group IV) units. There are striking differences between the group IV units in the median and the post-arterial articular nerves innervating the cat's knee joint.\textsuperscript{148,149} In the median articular nerve, in the normal joint, a large fraction of group IV units are mechanically sensitive, while, in the posterior articular nerve (PAN), less than 10% are sensitive. Group III units in both nerves have similar mecanosensitivity. Group IV units in the PAN, thus, contribute very little to sensory input in the normal joint, but are readily activated in inflamed joints.

Based on their response behaviors to passive innocuous and noxious joint movements, the fine afferent fibers in the medial articular nerve of the knee have been classified into four categories:\textsuperscript{148,149} 1) units that are excited by innocuous movement of the knee joint; 2) units that are only weakly excited by innocuous joint movements, while noxious movement leads to pronounced discharges; 3) units that respond consistently only to noxious joint movements; and 4) units that cannot be excited by any joint movement. In the normal knee joint, more than 70% of the unmyelinated afferents in the medial articular nerve have high activation thresholds for movements (fig. 3). About half of the fine myelinated afferents, however, respond to non-noxious movements. It is suggested that category 0 afferent might contribute to deep pressure sensation, while category 2 and 3 afferents contribute to joint pain.\textsuperscript{149} The category 4 afferents appear to play an important role in the pain and hyperalgesia associated with joint inflammation (see section on Sensitization of Joint Nociceptors).
PERIPHERAL MECHANISMS OF PAIN

Nociceptors in Cornea and Teeth. Although pain is generally thought to be the only sensation elicitable from the cornea and the tooth pulp, some studies have suggested that thermal, noxious, and mechanical stimuli can be differentiated on the cornea, and sensations other than pain can be evoked by tooth pulp stimulation. The cornea and the tooth pulp are unique in that they are innervated only by free nerve endings. The innervation density of intra-epithelial nerve terminals in the cornea is about 300–600 times that of the skin and 20–40 times that of the tooth pulp. In the cornea, the majority (72%) of the nociceptors respond only to mechanical stimulation, 17% respond only to cooling, and 11% are bimodal responding to mechanical and warming stimuli. The afferents for the mechanically sensitive nociceptors have conduction velocities in the C-fiber and A-delta fiber range, while the thermal receptors have afferents only in the C-fiber range. The mechanically sensitive nociceptors in the cornea, unlike those in the skin, have continuous receptive fields that usually cover 5–10% of the corneal surface. The tooth pulp is also innervated by A-delta and C-fibers, and their receptors are polymodal, responding to a variety of stimuli, including electrical, thermal, osmotic, and pharmacological agents.

Hyperalgiesia and Sensitization of Nociceptors

Hyperalgiesia is the perceptual companion of inflammation, be it from infection, abrasion, burn of the skin, or certain nerve injuries. Hyperalgiesia is an altered state of sensibility, characterized by a decrease in pain threshold, an increase in pain to suprathreshold stimuli, and, often, spontaneous pain. Lewis identified two distinct types of hyperalgiesia: primary and secondary hyperalgiesia. Primary hyperalgiesia refers to changes that occur within the site of injury, whereas secondary hyperalgiesia refers to changes that occur in the area surrounding the site of injury. Within the zone of a cutaneous injury induced by heat, mechanical injury, or by injection of noxious chemicals, hyperalgiesia is present to both heat and mechanical stimuli. This dissociation of mechanical and heat hyperalgiesia in the area surrounding an injury suggests that the neural mechanisms for these sensations are different.

Mechanism of Primary Hyperalgiesia

An obvious question is whether hyperalgiesia can be explained by commensurate changes in the sensitivity of cutaneous nociceptors. Sensitization of nociceptors is the neurophysiological correlate of hyperalgiesia, and is characterized by a decrease in threshold, an augmented response to suprathreshold stimuli, and, occasionally, by spontaneous activity. Sensitization of C-fiber and A-fiber nociceptors to heat stimuli after injury has been observed.

Fig. 4. Measurements of mechanical and heat sensitivities in the areas of primary and secondary hyperalgiesia following burns to the glabrous skin of the hand. Hyperalgiesia to mechanical stimuli was observed in both areas; hyperalgiesia to heat stimuli was observed only in the primary area. A. Mechanical thresholds for pain and ratings of pain to heat stimuli were recorded at sites A, B, and C before and after burns at sites A and D. Each burn consisted of a 53°C, 30-s stimulus. The areas of flare and mechanical hyperalgiesia following the burns in one subject are also shown. B. Mean mechanical thresholds for pain before and after burns are shown for seven subjects. The mechanical threshold for pain significantly decreased following the burn. The mechanical hyperalgiesias were of similar magnitude at each of the three test spots (A, B, C). Error bars correspond to SEM. C–E. Mean normalized ratings of painfulness of heat stimuli (same as in fig. 1) before and after burns are shown. C. At site A, all the characteristics of thermal hyperalgiesia (i.e., decrease in pain threshold, increased response to suprathreshold stimuli and spontaneous pain) were observed after the burns (N = 8). D. At site B, pain ratings decreased after the burns (N = 9). E. At site C, pain ratings before and after the burns were not significantly different (N = 8). From Raja SN, Campbell NJ, Meyer RA: Evidence for different mechanisms of primary and secondary hyperalgiesia following heat injury to the glabrous skin. Brain 107:1179–1188, 1984, with permission.
To determine which nociceptors code for primary hyperalgesia, Meyer and Campbell performed a correlational analysis of psychophysical studies of hyperalgesia in humans with responses of A-fiber and C-fiber nociceptors in monkeys (fig. 5). Identical test heat stimuli ranging from 41° C to 49° C were presented to the glabrous skin of the hand in humans and monkeys before and after a heat injury. The injury stimulus was a 53° C, 30-s burn which led to prominent primary hyperalgesia within minutes, characterized by augmented pain from both mechanical and heat stimuli. Following the burn, the heat threshold for type I AMHs was greatly decreased and the response to suprathreshold stimuli was increased. Similar sensitization of AMHs by heat was reported by other investigators. In contrast, the CMHs showed an increased heat threshold and a decreased response to suprathreshold stimuli following the burn. Similar lack of sensitization of CMHs innervating monkey glabrous skin was observed by others. These data suggest that type I AMHs, not CMHs, code for the thermal hyperalgesia that follows a burn to the glabrous skin.

Whereas sensitization to heat of the AMH nociceptors accounts for the heat hyperalgesia, sensitization to mechanical stimuli has not been observed after an injury either for AMHs or CMHs. However, Thalhammer and LaMotte have observed that the receptive fields of some CMHs and AMHs spread into the area of injury. Thus, a mechanical stimulus within the area of injury will elicit a response in more nociceptors than before injury. This spatial summation may account for the mechanical hyperalgesia at the site of injury. Another possibility is that an as yet unidentified nociceptor may be responsible for mechanical hyperalgesia.

The above observations that CMHs that innervate glabrous skin do not sensitize following a heat injury caused some confusion concerning the role of CMHs, in view of earlier observations that CMHs may, in certain instances, sensitize to heat. This issue appears to have been resolved by the finding that sensitization of CMHs in monkeys varies with skin type. The CMHs that innervate hairy skin sensitize readily, while those that innervate the glabrous skin of the hand do not sensitize, regardless of the heat stimuli used. The observation that CMHs innervating hairy skin sensitize lends credence to the view that CMHs may play a role in primary hyperalgesia to heat in hairy skin.

**MECHANISM OF SECONDARY HYPERALGESIA**

Both peripheral, and central mechanisms have been suggested in the past to explain secondary hyperalgesia. Lewis proposed that secondary hyperalgesia was due to...
a peripheral mechanism resulting from the spread of sensitization from adjoining nociceptors which were directly injured. According to this hypothesis, activation of part of the nociceptive receptor by the injury stimulus leads to antidromically propagated action potentials in other branches of the afferent, resulting in the release of sensitizing substances. This hypothesis is based on Lewis’ observation that electrical stimulation of the peripheral nerve causes hyperalgesia in the distribution of the nerve. A similar axon reflex mechanism is thought to account for the flare that surrounds an injury.151

In support of Lewis’ spreading sensitization hypothesis, Fitzgerald reported that adjacent injuries and antidromic electrical stimulation of the peripheral nerve in rabbit results in sensitization to heat of C-fiber nociceptors.68 Several authors have attempted to replicate this observation in other species, including primate, without success.106,190,213

Because psychophysical studies indicate that secondary hyperalgesia is characterized by hyperalgesia to mechanical stimuli, future neurophysiological studies should focus on the change in mechanical sensitivity following an injury. Studies in monkey have failed to demonstrate a change in the mechanical threshold of A-fiber or C-fiber nociceptors following a heat injury adjacent to their receptive field.212 However, it has been recently observed that A-fiber, but not C-fiber, nociceptors in rat developed a lower mechanical threshold in an uninjured part of their receptive field close to an area of mechanical injury.189 Whether this sensitization occurs in other species as well, and is sufficient to account for secondary hyperalgesia, remains to be proven.

Several recent experiments provide evidence that secondary hyperalgesia is due, at least in part, to a peripheral mechanism: 1) the secondary hyperalgesia surrounding an intradermal injection of capsaicin does not spread beyond a narrow strip of skin made anesthetic by intradermal injection of xylocaine,1 and 2) the pain perceived from infrascular electrical stimulation in awake humans is not altered by a cutaneous injury in the distribution of the fascicle. It has been argued that if secondary hyperalgesia was due to a central mechanism, the pain from electrical stimulation would increase after the cutaneous injury. As a result of these observations and the lack of evidence for sensitization to mechanical stimuli of conventional CMH nociceptors, it has been speculated that a nociceptor yet to be identified accounts for secondary hyperalgesia.155 This nociceptor probably does not respond to the normal mechanical or heat search stimuli used in typical neurophysiological experiments, but develops a mechanical sensitivity after injury. Although anecdotal observations of nociceptors which do not respond initially to mechanical stimuli have been reported, it is difficult to study this class of nociceptors, since they cannot be found using standard search procedures. A novel technique for identifying these nociceptors has recently been reported.184

Hardy and his colleagues were unable to replicate Lewis’ antidromic stimulation experiments and, therefore, postulated that secondary hyperalgesia may be due to changes in the central nervous system.91 According to their hypothesis, input to the dorsal horn from sensitized nociceptors in the area of injury leads to a “sensitization” of dorsal horn neurons that receive input from the skin surrounding the region of injury. This sensitization could be due to a facilitation of response of nociceptive neurons to nociceptive input, or it could be due to enhanced synaptic efficacy between central nociceptive neurons and low threshold mechanoreceptors.

In support of a central mechanism for secondary hyperalgesia, sensitization of dorsal horn spinohalamic neurons to mechanical stimuli following cutaneous heat injury and C-fiber stimulation has been demonstrated.95,116 In addition, Woolf demonstrated, in a chronic decerebrate rat preparation, that a cutaneous thermal or chemical injury resulted in a fall in mechanical threshold and thermal response latency of the hind limb flexion withdrawal reflex at the site of injury, as well as adjacent to the injury.256,257 This facilitation of the flexion reflex by tissue injury or C-fiber stimulation was independent of changes in the excitability of the terminals of primary afferents in the dorsal horn and of the motor neurons.46 In addition, marked expansion of the receptive field, often to the contralateral limb, was observed. Local anesthetic injected in the ipsilateral foot failed to alter the injury-induced contralateral receptive fields, suggesting an enduring central basis for the hyperalgesia. Further evidence of a contribution of the central nervous system stems from the observation that the spread of hyperalgesia to the contralateral paw in rat after a heat injury could be prevented by spinal anesthesia administered a few minutes following the injury.46 In addition, brief C-fiber strength conditioning stimuli were shown to produce a substantial increase in the size of the receptive fields of dorsal horn neurons.45 Some of the dorsal horn neurons that initially responded only to noxious mechanical stimulation responded to low threshold (brush and touch) stimuli following the conditioning stimuli (fig. 6). Thus, activity in C-fibers modifies the response properties of dorsal horn

neurons. It still remains to be determined whether this change is a result of increase in synaptic efficacy of excitatory inputs or a decrease in tonic inhibition.

Thus, secondary hyperalgesia is probably mediated by changes both in the peripheral and central nervous systems. Clearly, further work needs to be done to clarify these mechanisms.

Sensitization of Joint Nociceptors

Acute experimental arthritis has been induced in the cat's knee joint by injection of kaolin and carrageenan into the joint. When these animals are lightly anesthetized, movements in the normal working range of the joint produce a reflex increase in blood pressure and heart rate. Recordings from fine joint afferents in these animals reveal the following changes from the patterns seen in normal joints: 1) resting activity is more commonly observed and occurs at higher rates than in normal joints, 2) the background activity often consists of bursts of discharge, 3) sensitivity to movement in the normal working range of the joint is observed in more than 70% of fine afferents compared to less than 30% in normal joints (fig. 3).49,83,84 and 4) in the inflamed joint, units activated only by intense joint movements or not activated by movements (categories 3 and 4 of fine joint afferents) are rare. In contrast, in the normal joint, about 70% of the unmyelinated afferents belong to categories 3 and 4. This indicates that, as a result of inflammation, the high-threshold afferents are sensitized and now respond to movement in the normal working range of the joint. The increased sensitivity to movement manifests itself either as reduction in threshold, or enhancement of movement-induced responses, or both. These changes have been observed in both myelinated and unmyelinated afferents. Similar observations have been made in rat experimental models of acute or subacute polyarthritis induced with systemic administration of Freund's adjuvant.80

The inflammation-induced changes in response properties of fine articular afferents are thought to be due to the sensitizing actions of chemical mediators on their receptive terminals. The evidence for the role of bradykinin and metabolites of arachidonic acid will be discussed in the next section.

Biochemical Mechanisms of Hyperalgesia

Inflammation following tissue injury is associated with the release of several chemicals, including bradykinin, substance P, histamine, prostaglandins, thromboxanes, and leukotrienes. Many observations point to the involvement of bradykinin, PGs, and related compounds in the inflammatory response (for reviews and monographs, see references 33, 50, 70, 83, 135, 140–171, 187, 225, 235).

PAIN AND HYPERALGESIA OF INFLAMMATION: ROLE OF CHEMICAL MEDIATORS

The pain-producing properties of several endogenous vasoactive substances were studied extensively by Keele and Armstrong. By applying substances to blister bases in volunteers, they showed that pain was produced by peptides such as angiotensin, bradykinin, and substance P, and amines such as 5-hydroxytryptamine, serin, and various inflammatory exudates. Considerable evidence has since been presented that some of these substances, especially bradykinin and eicosa-
noids, promote the pain and hyperalgesia associated with inflammation.\textsuperscript{238}

Bradykinin and 5-Hydroxytryptamine. Bradykinin and 5-hydroxytryptamine (5-HT) are two endogenous substances released following tissue injury that are capable of evoking pain when applied to a blister base, even at very low concentrations.\textsuperscript{114} Bradykinin is present in inflammatory exudates,\textsuperscript{53,150,191} and produces pain in man when given intradermally, intra-arterially, or intraperitoneally.\textsuperscript{36,48,59,61,81,144} Both 5-HT and bradykinin are capable of eliciting nociceptive reflexes in experimental animals when administered intra-arterially.\textsuperscript{145} A reflex rise in blood pressure is elicited following the injection of bradykinin in the dog knee joint,\textsuperscript{160} or on the surface of the dog heart.\textsuperscript{218} Single fiber recordings from peripheral nerves have also shown that bradykinin administered intra-arterially or intradermally in the region of the receptive field of unmyelinated nociceptive afferents enhances the response to noxious heat stimuli (fig. 7).\textsuperscript{9,88,99,100} In contrast, 5-HT does not have a facilitatory effect on heat-induced spike discharges of the CMHs.\textsuperscript{9} Thus, neurophysiological evidence suggests that bradykinin, and not 5-HT, is an important mediator of the pain and hyperalgesia of inflammation.

Some recent observations, however, indicate that bradykinin is probably not the sole agent mediating the pain and hyperalgesia associated with inflammation. The concentration of bradykinin that has been detected in inflammatory exudates is low. Moreover, the concentrations of bradykinin in synovial fluids from patients with rheumatoid arthritis do not correlate with the severity of the symptoms in these patients.\textsuperscript{150} Bradykinin, however, is capable of stimulating the synthesis and release of PGs by activation of phospholipase A\textsubscript{2}.\textsuperscript{106,133} It has been suggested that the pain and hyperalgesia associated with inflammation is dependent on the potentiation of the effects of bradykinin by PGs.\textsuperscript{167}

Prostaglandins, Thromboxanes, and Leukotrienes. The prostaglandins, thromboxanes, and leukotrienes constitute a large family of compounds which are all oxygenated derivatives of arachidonic acid, an essential polyunsaturated fatty acid. The term “eicosanoids” is often used to embrace all the products of arachidonic acid metabolism.\textsuperscript{47}

Free arachidonic acid is the precursor of most mammalian prostaglandins. Arachidonic acid can be metabolized to the prostaglandin endoperoxides (PGG\textsubscript{2} and PGG\textsubscript{2}) by the enzyme cyclooxygenase (prostaglandin-

| **Fig. 7. Sensitization of an unmyelinated cutaneous nociceptive afferent in cat to noxious heat stimuli by bradykinin. Each dot represents the integrated number of spikes elicited by heating the skin to 45\textdegree C for 10 s at intervals of 1 min. The response of the unit before and after the intradermal administration of bradykinin (BKN) 10 \mu g is illustrated. Adapted from Beck PW, Handwerker HO: Bradykinin and serotonin effects on various types of cutaneous nerve fibers. Pflugers Arch 347:209-222, 1974, with permission.** |

synthetase) that is present in most cells (fig. 8). These are converted either enzymatically or non-enzymatically to prostacyclin (PGI\textsubscript{2}), thromboxane A\textsubscript{2} (TXA\textsubscript{2}), and the stable prostaglandins—PG\textsubscript{E\textsubscript{2}}, PGF\textsubscript{2\alpha}, and PGD\textsubscript{2} (for details of metabolic pathways, see references\textsuperscript{18,192,194,195}).

The alternate metabolic pathway for arachidonic acid is the lipooxygenase pathway. Lipooxygenase enzymes convert free arachidonic acid to hydroperoxy derivatives (HPETEs). Lipooxygenation at C-5 yields 5-s-hydroperoxyeicosatetraenoic acid (5-HPETE), which then undergoes enzymatic transformations to the biologically active leukotrienes. Oxidation at other positions yield a variety of mono- and dihydroxyeicosatetraenoic acids (HETeS) and their corresponding mono- and dihydroperoxyeicosatetraenoic acids (HPETEs) (for reviews, see references\textsuperscript{77,185,194,196,211,233,235}). Leukotrienes, HPETEs, and HETEs can be generated by a wide variety of cells at the site of inflammation.\textsuperscript{72}

Some indirect lines of evidence suggest a role for the eicosanoids in the process of inflammation. The eicosanoids occur in abundance in and around inflamed tissue.\textsuperscript{35,60,78,109} For example, prostaglandin E\textsubscript{2}, PGF\textsubscript{2\alpha}, PGI\textsubscript{2}, and thromboxane A\textsubscript{2} have been detected in inflammatory exudates induced by implantation of carrageenan-impregnated sponges under the skin of rats.\textsuperscript{35} Prostaglandins also occur in synovial fluid removed from the paws of rats with Streptococcus-extract-, carrageenan-, or adjuvant-induced arthritis, as well as from the joints of human rheumatoid or osteoarthritis sufferers.\textsuperscript{22}

Prostaglandins and related substances, in concentrations likely to be found at inflamed sites, do not cause overt pain, but, rather, hyperalgesia.\textsuperscript{41,42,60,63,102,107,206} In human subjects, intradermal injections or blisterbase applications of PGs and leukotrienes are not usually associated with pain.\textsuperscript{27,50,207} but the edematous area becomes hyperalgesic to touch.\textsuperscript{110,206} Subdermal PGE\textsubscript{1} potentiates the pain produced by subdermal histamine.
and bradykinin. The most potent PGs in this respect are PGI₂ (prostacyclin) and PGE₂. Prostaglandins have also been observed to produce prolonged hyperalgesia when injected in the rat paw. It has been suggested that this PG-mediated hyperalgesia is a cAMP/Ca²⁺ mediated process. The PGs, thus, must be considered to be different from other inflammatory mediators, because their principal role appears to be to enhance the inflammatory effects of other mediators, such as vasoactive amines and kinins. When given intradermally or intramuscularly in concentrations higher than those that occur in inflammation, PGE₂ causes long-lasting pain.

Several studies in experimental animals provide additional evidence that prostaglandins induce hyperalgesia and sensitize nociceptors to the effects of bradykinin.
and other amines. The potentiating effects of PGs to nociceptive reflexes induced by bradykinin have been demonstrated in several experimental preparations—the dog spleen, the dog knee joint, the dog heart, and the rabbit ear. Electrophysiological studies of cutaneous nociceptive afferents have provided more direct evidence for the sensitizing effects of prostaglandins on unmyelinated nociceptors, as well as A-delta mechanoreceptors. Continuous intrarterial infusions of PGE₁ and PGE₂ sensitize C-nociceptors and intensify bradykinin-induced discharges of these afferents.

Prostaglandin-induced hyperalgesia is more potent than that produced by PGE₂, but its effect is of shorter duration. In several experimental models, the hyperalgesia induced by PGE₁ and PGE₂ had a delayed onset, and lasted for more than 3 h. In contrast, prostacyclin (PGI₂) induces an early plateau (reached within 15–30 min) and a relatively short-lived hyperalgesia disappearing in less than an hour. The relative role of prostacyclin and other PGs in the hyperalgesia of inflammation is uncertain.

The effects of lipooxygenase products and leukotrienes on inflammatory pain are less well understood. Recent studies demonstrate that the production of leukotrienes is increased after mechanical or thermal trauma in rats. Leukotrienes have been detected in plasma and bile at levels sufficient to induce known phenomena associated with trauma, such as tissue edema and circulatory and respiratory dysfunction. Leukotriene B₄ also induces hyperalgesia in rats of a magnitude similar to that elicited by bradykinin and PGE₂. The LT₄-induced hyperalgesia, unlike that of bradykinin and PG₄, is dependent on the presence of polymorphonuclear leukocytes (PMNs) and independent of the cyclooxygenase pathway of arachidonic acid metabolism. Recently, LT₄ has been shown to produce thermal hyperalgesia in humans as well. When incubated with LT₄ in vitro, PMNs release a factor that induces hyperalgesia in rats that have been depleted of circulating PMNs. A recent study indicates that (8R,15S)-diHETE, a product of the 15-lipoxygenation of arachidonic acid, may be the factor that mediates the LT₄-induced hyperalgesia. Further proof for the involvement of the eicosanoids in inflammation stems from the observation that anti-inflammatory drugs suppress their biosynthesis. Most nonsteroid anti-inflammatory drugs inhibit the formation of PGs and thromboxanes by interfering with the cyclooxygenase. Anti-inflammatory steroids act at an earlier step by the formation of a polypeptide with an antiphospholipase effect. Thus, the release of arachidonic acid is blocked resulting in inhibition of the formation of not only PGs and thromboxanes, but also the leukotrienes. It is thus clear that arachidonic acid metabolites, prostacyclin and PGE₂ in particular, play an important role in the hyperalgesia that accompanies inflammation.

**Chemical Mediators of Arthritic Pain**

Similar to the changes in response properties of cutaneous nociceptors following injury to the skin, unmyelinated (group IV) and myelinated (group III) joint afferents have also been observed to sensitize following inflammation of joints. The changes in response properties of fine articular afferents to inflamed joints are thought to be due to the sensitizing actions of chemical mediators on their receptive terminals. It has recently been shown that PGs E₁ and E₂ induce changes in receptor properties of group III afferents from normal joints that are similar in character to those induced by inflammation. In units from inflamed joints, marked additional sensitization has been observed with small (<1 μg) doses of PGs (fig. 9). Aspirin and indomethacin, the cyclo-oxygenase inhibitors, depress the resting discharges and enhance movement-evoked activity of arthritic-joint capsule-receptors. Prostaglandin E reverses the depressing effects of aspirin and indomethacin on the spontaneous and evoked activity of fine afferents from inflamed joints. The long-lasting excitatory and sensitizing effects of PGs provide convincing evidence for the role of PGs in sensitization of joint afferents.

Other inflammatory mediators, such as bradykinin, serotonin, and histamine, also excite groups III and IV afferents, but not group II units. Histamine excites only those fine afferents which have ongoing activity, while...
bradykinin and serotonin activates all four categories of fine afferents that have been discussed earlier. The effects of bradykinin and serotonin are, however, of short duration, and tachyphylaxis is pronounced with repeated injections. It is, therefore, improbable that histamine, serotonin, or bradykinin play a major role in prolonged sensitization of joint receptors. Thus, pain of arthritis can be explained by enhanced responsiveness of group III and IV afferents, probably secondary to the release of chemical mediators such as prostaglandins.

Recent studies in rats with adjuvant-induced arthritis indicate that intraneuronal substance P (SP) contributes to the severity of joint inflammation. In rats with experimental arthritis, the concentration of SP increases in branches of peripheral nerves innervating inflamed joints.

Levine et al. have observed that joints which develop more severe arthritis are more densely innervated by SP-containing primary afferent fibers than joints which develop less severe arthritis. Moreover, infusion of SP into the joint cavity increases the severity of arthritis. Recent in vitro studies show that substance P stimulates, in a dose-dependent manner, the release of PG E2 from synoviocytes obtained from rheumatoid arthritis patients. The effect of substance P was specific as the release of PG E2 was reduced by substance P antagonists. Substance P, in addition, increased the proliferation of synoviocytes and stimulated the release of collagenase. Thus, the local release of substance P by peripheral afferent fibers in joints may contribute to the tissue destruction and pain associated with arthritis.

**Summary**

In the last two decades, considerable advances have been made in our understanding of the mechanisms of pain. Studies correlating subjective magnitude estimations of pain in man with activity in single nerve fibers in experimental animals, and microneurographic recordings in awake humans, have provided convincing evidence for the role of specific nociceptors and labelled lines for signalling pain sensation in the normal skin. The response properties of the different types of nociceptive afferents, both myelinated and unmyelinated, from skin, muscle, and joints make them ideal candidates for signalling pain sensations.

Cutaneous inflammation from any cause results in hyperalgesia. Cutaneous hyperalgesia at the site of an injury, i.e., primary hyperalgesia, can be explained by sensitization of nociceptors. This sensitization is likely due to local release of chemical mediators in the inflamed area. The metabolites of arachidonic acid (eicosanoids) and bradykinin appear to play an important role in the sensitization of nociceptors. Similar inflammation-induced changes in response properties of fine articular afferents might explain the pain of acute arthritis. The neuropeptide substance P released from primary afferents may also play an important role in the pathogenesis of arthritis. The mechanism of hyperalgesia in the region surrounding the injury, i.e., secondary hyperalgesia, is less well understood, and probably results from changes both in the peripheral and central nervous systems.

While considerable advances have been made in our understanding of the mechanisms of acute pain, the pathophysiology of most chronic pain states is still unclear. We hope that future studies in experimental animals, and careful psychophysical testing and microneurographic recordings in chronic pain patients, will lead to a better understanding of the pathophysiology of pain.

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**Appendix**

**Microneurography**

A new technique has been developed to measure in awake humans the activity of single cutaneous nerve fibers in response to adequate stimulation of their receptive fields. The neural activity evoked by natural and electrical skin stimuli is correlated with the subject's verbal report of the experienced sensation (refer to reference for details). In brief, the technique consists of the percutaneous insertion of microelectrodes into a fascicle of a peripheral nerve and recordings of activity from nerve fibers in close proximity to the electrode. Neural activity has been recorded from cutaneous fascicles of the median, radial, saphenous, and perineal nerves. Investigators using this technique believe that that the amount of nerve damage induced is minimal, since no long-lasting clinical symptoms are generally observed in volunteers in whom recordings have been made. The activity in groups or single myelinated and unmyelinated afferents, and even sympathetic efferent fibers have been recorded using this technique. Conduction velocity of the fiber can be determined by electrical stimulation at the receptive field. Moreover, the intrafascicular microelectrode can be used as a stimulating electrode, delivering electrical current pulses of a few nanoseconds into the nerve fiber. Different sensations can be elicited by direct stimulation of the nerve fibers bypassing the nerve endings. These correlative microneurographic/psychophysical studies help to determine if a particular receptor type contributes to a particular sensation, and whether stimulus-induced pain can be explained by discharge patterns of individual nociceptors.

In a recent critique of microneurography, evidence was
presented suggesting that the electrodes may cause pressure on the axons in the impaled nerve fascicles resulting in a temporary pressure block of the fibers. The authors, therefore, opined that the single units recorded were from one of the few fibers that survived the pressure block. If this were the case, the nerve from which recordings are made is in an abnormal state and, therefore, would be of limited value in studying sensory physiology. Recent studies provide evidence that an extensive pressure block is not a feature in microneurographic experiments.

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