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MECHANISMS OF FIRST AND SECOND PAIN IN THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS

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Brief (<2.0 sec) noxious heat pulses (peak temp = 51.5°C) programmed by a computer and generated by a contact thermode produced first and second pain in human subjects. Measurements of reaction time confirmed that these first and second pains were related to the conduction of impulses in Aδ heat nociceptive and C polymodal nociceptive afferents respectively. Estimates of psychophysical magnitude showed that when four identical heat pulses were applied to the same spot on the hand (interstimulus interval ≤ 80 sec), the first pain progressively decreased in perceived intensity whereas the second pain increased with interstimulus intervals of 3 sec or less. The first pain did not decrease if the location of the thermode was changed between each stimulus whereas the summation of the second pain increased under these conditions. Identical trains of noxious heat pulses partially suppressed the responses of Aδ and of C nociceptive afferents. These psychophysical observations and physiologic records indicate that the temporal suppression of heat-induced first pain is related to the suppression of Aδ heat nociceptors and that prolonged temporal summation of second pain is related to summation within the central nervous system. Aδ heat nociceptive afferents and C polymodal nociceptive afferents converge on two types of spinothalamic tract neurons: (1) wide dynamic-range neurons that receive input from non-nociceptive and nociceptive afferents, and (2) nociceptive-specific neurons. Since both types show summation of responses to repeated C fiber stimulation, they can account for summation of second pain.

Near the beginning of this century, Head [1] concluded that the skin is served by epicritic and protopathic afferent systems, each of which gives rise to its own particular types of sensations. Epicritic sensations are specifically localized, do not outlast the stimulus, and provide qualitative information about the stimulus. For example, epicritic pain can be elicited by a mild needle prick. In contrast, protopathic sensations are less well localized, slower in onset, and outlast the duration of the stimlus. Since protopathic pain is accompanied by a particularly unpleasant feeling and slowly mounts in intensity, it may be involved in the mechanisms of chronic pain and in some forms of pathologic pain such as postherpetic neuralgia and causalgia. Despite the controversies aroused by Head's theory of epicritic and protopathic sensibility, it is still used to describe skin sensations that occur before and after partial nerve blocks and after nerve division [1–3].

Both kinds of pain can be experienced when a brief noxious stimulus is applied to the distal part of an extremity. Often a sharp, well-localized first pain is followed 1 to 2 sec later by burning or throbbing pain [3–5] which is less well localized than the first, outlasts both the stimulus and the arrival of incoming primary afferent impulses, and becomes more intense with repeated application of the stimulus [3,4]. Thus, both the first and second kinds of pain have characteristics that are related to epicritic and protopathic sensibility respectively.

Our objective in this brief report is to account, at least in part, for the characteristics of these two forms of cutaneous pain in terms of the relevant primary afferent neurons, central neural mechanisms, and central neural pathways. We will compare the responses of the nociceptive neurons with the sensory experiences that are elicited by various types of noxious stimuli applied to the skin. The studies of first and second pain discussed here have been extremely useful in elucidating pain mechanisms. First, synchronous stimuli which evoke both kinds of pain help to identify the primary afferents, central pathways, and neural mechanisms involved in pain. Second, the brevity of the stimuli greatly reduces the chance of tissue damage and makes the suprathreshold pain more tolerable for experimental subjects. Finally, the relative intensities of first and second pain can be scaled and their qualities described with some uniformity [3–5].

PRIMARY CUTANEOUS AFFERENTS

The nociceptive receptors that signal impending tissue damage are not uniformly sensitive. They

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fall into several categories depending on their responses to mechanical, thermal, and chemical stimulation of the skin and on the conduction velocities of the axons that supply them [6]. Three major classes of primary afferent neurons which have been extensively studied are strongly implicated in pain mechanisms. Their essential characteristics are summarized in the Table and are described below.

Aδ high-threshold mechanoreceptive afferents (HTM) which respond only to intense mechanical stimuli and conduct between 4 and 40 m/sec have been described in the skin of the cat and in monkey extremities [6–8]. Many respond only to stimulus intensities that produce overt tissue damage, others give threshold responses to nondamaging pressure applied to the skin (less than 1 gm/cm^2). Most important, all such primary mechanoreceptive afferents respond to noxious or potentially damaging skin stimuli with the highest impulse frequency. They have small receptive fields and are particularly sensitive to excitation by sharp objects. They are relatively insensitive to heat stimuli, though they sometimes respond to noxious heat after repeated exposures. Therefore, they seem well adapted for transmitting information which is related to the localized pricking pain produced by mechanical stimuli.

Aδ heat nociceptive afferents conducting between 3 and 20 m/sec have recently been identified in the limb and facial skin of monkeys [6,8–10]. Like the Aδ high-threshold mechanoreceptive afferents, these afferents have small receptive fields and respond to intense mechanical stimulation. However, unlike the Aδ high-threshold mechanoreceptive afferents, Aδ heat nociceptive afferents respond monotonically to increases in receptive field skin temperature [10]. These responses accelerate positively, the steep portion of the curve occurring in the 45 to 53°C range. Threshold temperatures for these afferents are usually below noxious or painful levels (40–44°C), but highly noxious skin temperatures >50°C) evoke maximum responses. The role of these neurons in signalling pain is clearly established. They are the only myelinated primary afferents innervating the skin of the extremities that can be reliably activated by noxious heat. Thus, heat-induced first pain, whose latency corresponds to the activity in the small myelinated Aδ fibers, must be initiated by impulses in the Aδ heat afferents. Neither this first pain nor the responses of the Aδ heat afferents outlast the duration of the heat stimulus. Both the intensity of the first pain in man and the responses of the Aδ heat afferents in monkeys are progressively reduced during brief repeated application of heat stimuli to the same spot on the hand (Fig. 1) [4]. Therefore, the characteristics of heat-induced first pain can be largely accounted for by the response characteristics of Aδ heat nociceptive afferents.

Recently we have found that these same afferents excite neurons in the spinothalamic tract of monkeys that are likely to be involved in pain (Price, Hayes, Ruda, and Dubner, unpublished observations) and thereby demonstrated that these primary afferents have central connections consistent with a role in pain.

C polymodal nociceptive afferents form an extremely important group of peripheral fibers since they constitute 80 to 90% or more of the C fiber population of primates [8,11,12]. They innervate the skin of the cat [13], monkey [8,11], and man [12,14] and are characterized by their responses to noxious mechanical, noxious heat, and chemical irritant stimuli. Some also respond to intense cold (<10°C) [8]. These polymodal nociceptive afferents have several important properites such as sensitization to repeated applications of low-intensity noxious stimuli [13] and response suppression by high-intensity noxious stimuli [11]. They respond with their highest frequency to two or more forms of intense cutaneous stimuli, but also respond weakly to mechanical (1–10 gm) and thermal 38–43°C) stimuli that are clearly not painful to human observers. They may, therefore, provide some information about nonpainful sensations.

There is little doubt that C polymodal nociceptive afferents signal tissue damage and contribute directly to pain sensations. Brief noxious stimuli evoke not only first pain but also a delayed second pain, whose latency can be accounted for only on the basis of impulses conducted over unmyelinated C fibers. The latency to second pain is a direct function of the peripheral conduction distance [3,4]. These second pains can be evoked even after selective blocking of the first pain. Brief heat pulses evoke distinct first and second pains. Ex-

TABLE 1. *Primary afferent neurons subserving first and second pain*

Primary afferent category	Conduction velocity range	Mechanical response range		Thermal response range		Relation to first and second pain
		Non-noxious	Noxious	Warming	Noxious	
Aδ high threshold mechanoreceptive afferent	4–40 m/sec	+	++	–	+*	First pain mechanically induced
Aδ heat nociceptive afferent	3–20 m/sec	+	++	+	++	First pain mechanically or thermally induced
C polymodal nociceptive afferent	0.5–2.0 m/sec	+	++	+	++	Second pain mechanically or thermally induced

+ = Weak response; ++ = strong response; * = after repeated exposure to noxious heat.

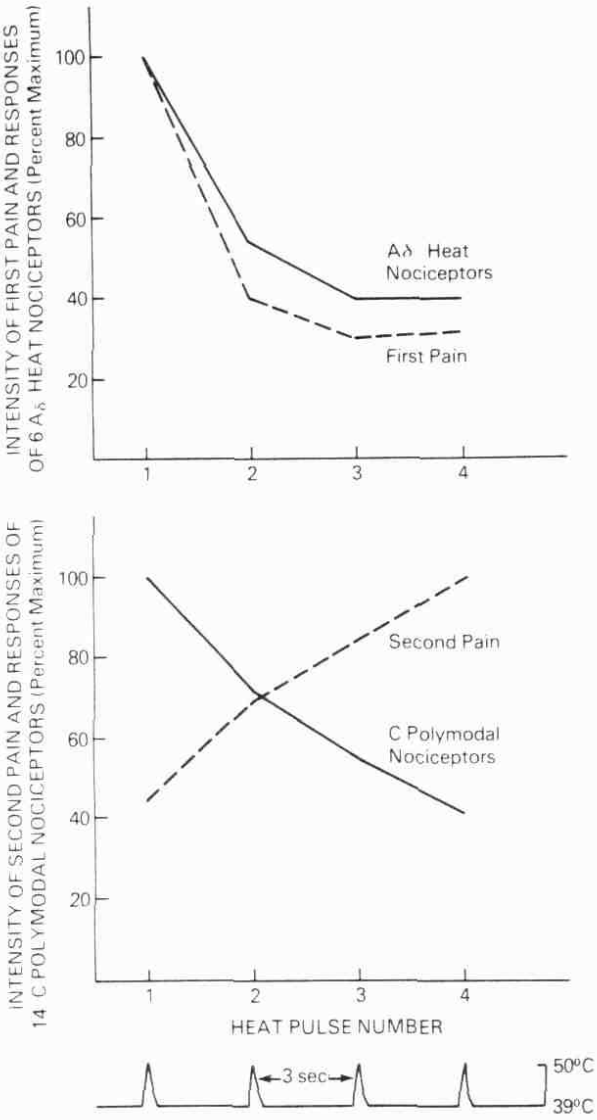

FIG. 1. *Top:* Heat pulse-induced first pain (man) compared with cumulative responses of 6 Aδ heat nociceptive afferents (monkey). The constant waveform heat pulses applied to the skin are shown at the bottom. The interval between heat pulses is 3 sec. The curves of first pain and Aδ heat nociceptor suppression are similar (data adapted from [4]). *Bottom:* Heat pulse-induced second pain compared with cumulative responses of 14 C polymodal nociceptive afferents. Note that second pain intensity summates even though the same train of heat pulses progressively suppresses the responses of C polymodal nociceptors.

cept for the very small population of C warm afferents that respond to noxious heat [15], polymodal nociceptive afferents are the predominant C afferent group activated by this stimulus in primates and are the peripheral population most likely accountable for heat-induced second pain.

Like the responses of Aδ heat nociceptive afferents, those of C polymodal afferents became progressively reduced in monkeys during a train of heat pulses (interpulse interval = 3 sec; see Fig. 1, *bottom*). If an identical train of heat pulses is applied to the hands of human observers, second pain *summates* in intensity (Fig. 1, *bottom*). Thus, second-pain summation occurs when the afferents evoking it are partially suppressed and must be critically dependent on prolonged summation in the central nervous system. This explanation is supported by the observation that second pain summates to an even greater extent when the location of the probe on the skin changes between successive heat pulses so that different receptors are activated with each stimulus [4]. The duration of second pain also extends beyond the arrival of incoming C fiber impulses. Experimentally induced second pain, some forms of chronic pain, and some pathologic pain states are all characterized by summation and sensations outlasting stimulation [1–4].

C polymodal nociceptive afferents excite many of the same spinothalamic tract neurons that are activated by Aδ heat nociceptive afferents [16, and unpublished observations]. Therefore, they have central synaptic connections adapted to play a role in pain mechanisms.

CENTRAL NOCICEPTIVE NEURONS

It has often been suggested that pain perception and nociceptive reflexes are not directly and simply related to activity evoked in "pain" receptors but depend on several integrative mechanisms of central neurons [17], for example, the evident lack of a simple one-to-one relationship between C polymodal nociceptive responses and second pain. The objective of this section is to account for some aspects of pain perception that cannot be explained by the responses of primary afferent neurons. This explanation focuses on the characteristics of spinothalamic tract neurons that could be involved in first and second pain. Three distinct types of spinothalamic neurons that could convey information about first and second pain are given in Figure 2. These neurons, which are found in the monkey in the dorsal horn of the spinal cord grey matter, are in synaptic contact with primary afferents and relay information about touch, pain, and temperature to the thalamus.

Wide dynamic range neurons are concentrated mainly in laminae 5 of the dorsal horn and receive synaptic excitatory effects from large, myelinated (Aβ), low-threshold mechanoreceptive afferents (LTM), Aδ heat nociceptive afferents, Aδ high-threshold mechanoreceptive afferents (HTM), and C polymodal nociceptive afferents [16,18]. As a result of this extensive convergence, these cells respond with increasingly higher frequencies of impulse discharge to touch, firm pressure, and noxious pinching. The responses of many of these cells are monotonic functions of increases in skin temperature within the noxious range (44–52°C), similar to the perceived magnitude of pain intensity over this same temperature range [19].

However, the impulse discharge frequencies evoked in these neurons by skin stimulation are not always simple direct functions of impulses in primary afferents, but are subject to local inhibitory and facilitatory mechanisms and to strong descending controls [17,20]. For example, stimula-

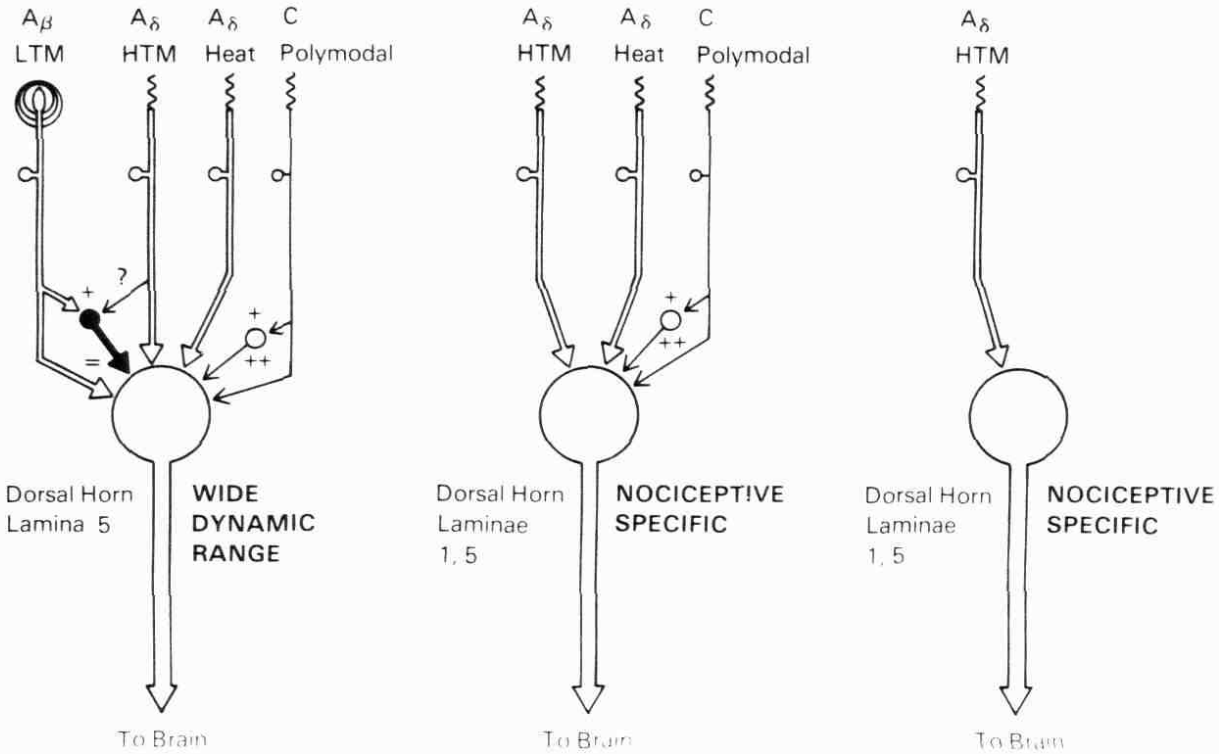

FIG. 2. Three types of nociceptive neurons in the spinothalamic tract of the spinal cord. Inhibitory interneurons are designated in *black* and by *minus signs* at their synapses. Facilitatory interneurons are indicated by *small unfilled circles* and *plus signs*. *LTM* = Low-threshold mechanoreceptor, *HTM* = high-threshold mechanoreceptor.

tion of many low-threshold mechanoreceptive afferents at high frequencies will reduce their responses to noxious stimulation [20]. These interneuronal inhibitory mechanisms are shown in Figure 2.

The responses of these wide dynamic range neurons to noxious stimuli of brief duration show a clear analogy to first and second pain. Brief noxious stimuli evoke a brief-latency, high-frequency impulse discharge which is related to the impulse input from myelinated A fibers and delayed lower-frequency discharge related to the impulse input from C fibers [16,21]. The first response, like first pain, does not outlast the arrival of the peripheral impulses but with each successive stimulus, either decreases in magnitude or stays the same. The delayed response, like second pain, long outlasts the arrival of incoming C impulses and increases in frequency and duration with each successive stimulus. This summation, like second pain. occurs only if the interstimulus interval is 3 sec or less. Thus it is evident that C fiber impulses activate central facilitatory mechanisms in the dorsal horn (Fig. 2).

The second type of dorsal horn spinothalamic neuron is relatively specific for responses to intense mechanical and thermal stimuli (Fig. 2, *middle*). It receives excitatory synaptic effects from high-threshold Aδ mechanoreceptive afferents, from Aδ heat nociceptive afferents, and from C polymodal nociceptive afferents [16]. As a result of these inputs, this type of neuron responds to firm pressure and pinch with an increasingly higher frequency of impulse discharge. Some also respond to noxious skin temperatures. Its responses to brief noxious stimuli are very similar to those of wide dynamic range neurons and therefore show parallels to first and second pain.

The third type of dorsal horn spinothalamic neuron is unequivocally specific for responses to noxious skin stimuli (Fig. 2, *right*). It appears to receive input from only Aδ high-threshold mechanoreceptive afferents since it responds only to noxious mechanical stimulation of the skin or to electrical stimulation of the Aδ afferents [16]. Its responses do not outlast the stimulus nor do they summate with repeated application. Therefore, like the Aδ primary afferent high-threshold mechanoreceptors, this type of neuron is likely to be related to the first pain evoked by a needle prick.

SUMMARY AND CONCLUSIONS

The characteristics of first and second pain can be partially explained by the functional properties of primary afferent and spinothalamic tract neurons. First pain is likely to be related to the activation of Aδ high-threshold mechanoreceptive afferents and/or of Aδ heat nociceptive afferents whereas second pain is probably the consequence of impulses in C polymodal nociceptive afferents. The progressive suppression of heat-induced first pain with repeated stimuli is due to the suppression of Aδ heat nociceptive afferents. Unlike first pain, second pain outlasts the stimulus and summates with repeated stimulation, probably because of the interneuronal facilitatory mecha-

nisms activated in the dorsal horn by C fiber impulses. Spinothalamic neurons that convey information about first and second pain include (1) wide dynamic range neurons that receive input from low-threshold Aβ mechanoreceptive afferents and from Aδ and C nociceptive afferents, (2) nociceptive-specific neurons that receive input from Aδ and C nociceptive afferents, and (3) nociceptive-specific neurons that receive input from Aδ high-threshold mechanoreceptive afferents. Thus, many spinothalamic tract neurons appear to convey information about both first and second pain. The difference in the quality and intensity of the two types of pain may reflect the differences in impulse patterns generated in the same second-order neuron by inputs over Aδ and C nociceptive afferents.

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