Part I. Neuroanatomical Substrate of Pain

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Pain, one of man’s most worrisome afflictions, is also one of neurobiology’s most challenging problems. Even its definition is beset with controversy. The origin and current resolution of this controversy are presented in this paper, but the major purpose of Part I is to review the anatomical substrate of the peripheral and central nervous systems involved in pain. Structural and functional characteristics of pain receptors and their afferent fibers are described, with emphasis upon current hypotheses regarding putative neural transmitters and possible mechanisms for signal transduction. Hitherto unrecognized details of the cytoarchitecture, anatomical organization, and circuitry of the dorsal horns are reviewed. The paper concludes with a consideration of the major components of the ascending and descending systems of subserving pain.

Key Words: Neuroanatomy, Neurophysiology, Pain.

Among the greatest challenges facing today’s neurobiologist is that of unraveling the mysteries of pain. Although competent scientists have studied this problem over the centuries, more new knowledge has become available within the last decade than in all previous time. These remarkable advances result from the combined efforts of legions of investigators from multiple disciplines who are applying powerful new experimental tools and techniques. Any attempt to summarize and synthesize this multifaceted story must start with an understanding of what is meant by “pain.”

DEFINING PAIN

Mountcastle has said that “Pain is that sensory experience evoked by stimuli that injure or threaten to destroy tissue, defined introspectively by every man as that which hurts.” Everyone agrees that pain is an unpleasant experience. But is it a sensation or a feeling reaction?

There are at least two components involved in the sensation and perception of pain. One is the perception of actual or threatened tissue damage; another, an affective state of unpleasantness—giving pain its unique aversive quality. This pluridimensional character of pain has posed serious problems for studying it.

The Controversy: Specificity vs Nonspecificity

For centuries arguments have raged over whether pain is a separate, distinct sensation or just a feeling reaction.

Those believing in the specificity position held that the neural substrate for pain has unique anatomical and physiological properties. The perception of tissue threat or damage is pain. The adjunctive affective state is the reaction that follows; ie, pain arises before the affective mechanisms are activated—the affective state is a consequence of pain.

Those accepting the nonspecificity view believed that because of its affective component the sensation of pain requires the activation of neurons outside the somatovisceral pain pathways. The perception of tissue threat or damage is, by itself, not pain.

Why are these arguments important? Lack of general agreement on what comprises the pain neurons, pathways, or system impairs communication among neuroscientists, doctors, dentists, or therapists who must deal with chronic pain.
Resolution of the Controversy

The following list of observations have accumulated over the years to support the specificity view.3,19 Today most investigators agree that the receptors mediating pain sensation can be distinguished as a group distinct from other receptor types.18 Evidence supporting the specificity view:
1. The chronaxies (ie, the time constants for excitation) are different for pain and touch sensations.20
2. Pain is demonstrable earlier in ontogeny than are other modalities.19
3. Sciatic nerve lesions lead to a loss of pain for a smaller area than for loss of touch.21
4. Some pressure receptors never mediate pain even when stimulated at their maximum rate and capacity.21
5. Analgesic drugs can alter pain threshold by 35 to 80 percent without changing the threshold of the other somatic senses.13
6. Some regions of the body give rise only to pain sensation (for example, Kiesow's area opposite the second molar).21
7. The dermatomes for pain, temperature, and touch are not identical.22
8. During differential block of peripheral nerves, pain sensation may be blocked independently of the other sensations.23

Once the specificity view of pain was accepted, it was necessary to establish criteria for determining whether any given neuron was part of the pain system.3 Any peripheral or central neuron is considered to be part of the pain system if:
1. it responds exclusively to noxious stimuli,
2. it has anatomical connections with neurons that contribute to pain,
3. its stimulation elicits painful sensations, and
4. when its response to noxious stimuli is reduced, the sensation of pain is also reduced.

As will be seen, the foregoing criteria of evidence have been satisfied for a significant fraction of the unmyelinated C fibers,24–31 the finely myelinated Aδ cutaneous nerve fibers,31–35 the spinothalamic neurons in the dorsal horn,36–41 and certain neurons in the reticular formation,42–45 thalamus46–50 and cerebral cortex.51,53

The properties of neurons meeting these criteria for pain transmission will be examined in some detail in this series of articles. This information is not new to this journal's audience. The December 1978 issue of Physical Therapy was devoted to transcutaneous electrical nerve stimulation, and in the first paper, Dr. Steven Wolf reviewed the basic neuroanatomy of the ascending and descending systems of the CNS subserving pain sensation.50 I do not apologize for reiterating here some of the same basic information because a thorough understanding of the neural machinery is essential if new modalities for pain management are to be employed intelligently and effectively. My article considers peripheral as well as central neural mechanisms involved in pain and also examines in some detail the cytoarchitecture and neural circuitry of the dorsal horns.

PERIPHERAL SYSTEMS SUBSERVING PAIN

Pain Receptors

Today the functional role of virtually every receptor and its corresponding afferent fiber in the cutaneous sensory nerves of experimental animals has been established.31,35

Cutaneous receptors responsible for transducing noxious stimuli are described morphologically as "free" or "undifferentiated" nerve endings.31,34,35,54–57 However, there are no truly "free nerve endings." Axons in the dermis are enveloped by Schwann's cells; those in the epidermis are in close association with epidermal cells. These undifferentiated nerve endings are all similar or identical in structure. In other words, structural differences do not account for the functional specificity of receptors transducing noxious stimuli.

Some receptors respond only to noxious stimuli such as noxious mechanical stimuli or noxious thermal stimuli. These are called "unimodal nociceptors." Others respond not only to noxious stimuli but to chemical, mechanical, or intense thermal stimuli as well. These are called "polymodal nociceptors."27,31,57

In any given area there is marked overlap of the receptive fields of different afferent fibers. This is especially true for areas with a high innervation density such as the finger tips or perioral zone.22,35 Therefore, even minimal stimulus intensities must activate numerous types of receptors. Thus, the pattern of impulses generated in a cutaneous nerve is highly complex in terms of temporal and spatial patterns of discharge.18

Afferent Fibers in Peripheral Nerves

Electrical stimulation of man's peripheral nerves has revealed the involvement of two afferent fiber groups subserving pain.16,25,34,58,59 Activity in fine myelinated fibers of the Aδ pain group evokes sharp, pricking pain,5,31–35,60 whereas activity in slow nonmyelinated C fibers evokes a burning sensation.5,24–30,60 In response to single shocks, the Aδ pain is more severe than C-fiber pain. But C-fiber pain is more severe when the stimulation is repetitive.14 This ob-
Fig. 1. Proposed model for transmitter action at undifferentiated nerve endings (UNE).

Observation shows that C-fiber input summates. Strong C-fiber pain is thought to underlie suffering.33, 61

Obtaining recordings from peripheral nerves in man have recently become feasible. Results from such experiments have revealed that 100 percent of the unmyelinated C fibers respond to noxious stimuli in man, compared to 50 percent in the cat.29

Adequate stimulus for pain. “What is the adequate stimulus?” is a major question that arises about pain receptors. The answer is not known with any certainty but a current hypothesis gaining increasing support is as follows: Cutaneous undifferentiated nerve endings contain one or several chemical substances. This substance(s) may be within vesicles or granules. These substances are specific and are released in response to a particular stimulation. The released agent diffuses out of the nerve ending, combines with receptors on the external surface of the ending, and causes it to depolarize the ending. The action of the receptor substance is terminated by an appropriate enzyme surrounding the nerve terminals, as suggested by the scheme in Figure 1.

All sorts of substances have been proposed as likely receptor substances—including K⁺, histamine, bradykinin, somatostatin, substance P, and prostaglandins.5, 35 Until recently no one had been able to demonstrate the presence of such substances in peripheral nerve endings.

Putative receptor substances and neural transmitters. In 1975, however, Hokfelt and co-workers, using an antibody immunofluorescence technique, demonstrated the presence of substance P (an 11-amino acid peptide found in many areas of the nervous system) around somatic nerve endings.62 In addition, degrading enzymes were also discovered close to the nerve endings. Nonspecific cholinesterase was around somatic endings and specific cholinesterase was around visceral receptors.35

A current hypothesis proposes that each functional type of dorsal root cell elaborates its own specific receptor substance and transports it by axoplasmic flow from the cell body to its peripheral endings and probably to its central endings as well, where the substance serves as the neural transmitter of the primary afferent fiber (Fig. 2). In other words, the receptor substance and the neural transmitter of a sensory cell are assumed to be the same substance.

One putative transmitter of nociceptive neurons in the dorsal horn is substance P.63-73 Ten to 20 percent of the dorsal root ganglion cells contain substance P. Immunohistochemical methods have demonstrated that this peptide is localized in the marginal and gelatinosa layers of the dorsal horn, where the pain fibers terminate. In fact, all neurons in these regions, which are excited by Aδ and C fiber impulses, are also strongly excited by substance P.74, 75

An unanswered question, however, is “Why does the response of the second-order neurons to substance P have so long a latency?”

Other putative transmitters of the dorsal root ganglion cells have not yet been identified except for somatostatin, found in about 10 percent of the dorsal root ganglion cells.67

Sensitization. Most types of receptors are rendered less responsive if subjected to sustained stimulation except those serving pain. Following burns and other types of trauma, pain sensation persists. This phenomenon, peculiar to pain, is known as sensitization.27, 76-78 The hypothesis for this phenomenon proposes that tissue damage that causes the release of a receptor substance may at the same time destroy the degrading enzyme, resulting in a prolonged depolarization of the transducer membrane and persistent firing in the pain fibers.

Cytoarchitecture of the Dorsal Horns

Before we can consider how the primary afferent fibers terminate within the dorsal horns, we must first examine for a moment the cytoarchitecture of the...
Fig. 3. Hemisection of spinal cord showing Rexed's laminar designations for the spinal gray. 79, 80

According to Rexed, the dorsal horn is composed of V or VI laminae (Fig. 3). 79, 80 Lamina I is the marginal zone. It contains three types of cells. 31, 81-84 The most important for our argument are the marginal cells. 31, 85, 86 These are interneurons with large oval bodies and thick dendrites radiating parallel to the surface of the gray matter. Other dendrites are distributed in the marginal zone and the adjacent white matter and some penetrate laminae II and III. 31, 87, 88 The axons of the marginal cells run to the adjacent fasciculi proprii and perhaps in some cases to the contralateral spinothalamic tract. Because these neurons respond to noxious stimulation, they are considered to be nociceptive interneurons of the spinothalamic tract. Laminae II and III form the substantia gelatinosa, which contains two types of cells: 1) small inhibitory interneurons that make local inhibitory circuits and that are typical of local circuit or Golgi type II neurons for mediating "feedforward" inhibition and 2) large neurons that appear to project to the spinothalamic tract. 31, 89-91 Some neurons of the substantia gelatinosa have been seen with two axons. 92 The functional meaning of this unusual feature is unknown. Another unusual, but probably important, structure within lamina II is the glomeruli, each of which is composed of a large primary afferent ending with an accumulation of boutons, dendrites, dendritic spines, and all types of synapses. All of these components are enveloped in glial lamellae. 93-96 These structures are assumed to be involved in complex integrative processing, but how they are involved remains a question. Laminae IV to VI, the nucleus proprius or magnocellularis, is an area with vague boundaries and contains the largest cells of the dorsal horn with an admixture of medium and small cells. 97-101 The apical dendrites of the large cells project into the substantia gelatinosa. Some of them project to higher levels of the neural axis. The input to these large cells is poorly understood. They respond to noxious stimuli, but much less specifically than do the neurons of lamina I. For example, these neurons deep in the dorsal horn respond to light brushing as well as to noxious stimuli. Therefore, they are called "wide dynamic range neurons." 100

Anatomical Organization of Dorsal Root Fibers

About 1 mm outside the spinal cord, the large and small fibers in the dorsal roots, which are arranged randomly in the peripheral nerve, undergo a spatial rearrangement. 31, 102-106 The small myelinated and unmyelinated fibers carrying pain signals course to the periphery of an individual rootlet, as depicted in Figure 4. This lateral position makes them appropriately placed to enter directly into the tract of Lissauer.
Fig. 6. Ventral aspect of dorsal horn shown in a three-dimensional scheme. Note the wide distribution and preponderance of terminals of large fibers in comparison to those of small fibers.\textsuperscript{31}

where they run for one or two segments before penetrating the gray matter of the dorsal horn.\textsuperscript{31, 104}

The large primary afferent fibers assume a medial position in the dorsal root, entering the spinal cord and going directly into the dorsal columns.\textsuperscript{31, 102} The fibers form a large bundle that runs along the medial aspect of the dorsal horn (Fig. 4).

Years of work have gone into elucidating the termination of the primary afferent fibers within the dorsal horns.\textsuperscript{81, 89, 90, 93, 102-106} Some of this work is summarized in Figures 5 through 8.

The small primary afferent fibers terminate in lamina I, the marginal zone (Fig. 5). The large afferent fibers terminate in lamina II of the substantia gelatinosa. Before terminating, however, the large afferent fibers travel along the medial surface of the spinal gray matter, enter the gray matter deep in layers IV and V, and then turn to sweep up into layer II. Here they terminate in a flame-shaped tuft without penetrating the marginal layer.

The neurons within the substantia gelatinosa (laminae II and III) are arranged in vertical columns (Fig. 6). The flame-shaped terminals of the large fibers divide the gelatinosa into a series of lobules within which the gelatinosa neurons are arranged in vertical columns. The large neurons of lamina IV send apical dendrites into these lobules, in position to make synaptic connections with the large primary afferent terminals. These details of the terminations of the small and large primary afferents are shown in greater detail in Figure 7, A and B.

Despite all of these structural details concerning the terminations of the primary afferent fibers, the circuitry of the dorsal horn is not well known and, in fact, represents one of the important gaps in our knowledge of pain.

**Functional Organization of Circuity in Dorsal Horns**

So far only two basic circuits have been proposed.\textsuperscript{32, 81, 100, 103, 106-113} These circuits are shown schematically in Figure 8.

The input to the marginal cells is not a settled issue. The tract of Lissauer contains not only primary afferent fibers but axons of gelatinosa neurons as well.\textsuperscript{22, 102, 104, 114} After the tract is transected, the axosomal and axo-dendritic boutons on the marginal cells degenerate, showing that C fibers and gelatinosa neurons must terminate on them.

As discussed previously, C fibers terminate in the marginal zone and in the substantia gelatinosa. The C fibers are thought to make excitatory synapses on the dendrites of both the marginal cells and the substantia gelatinosa neurons. The substantia gelatinosa neurons in turn make inhibitory synapses on the

![Terminal Arborizations](image_url)

**Fig. 7.** Details of terminal arborizations of small fibers (A) and large fibers (B).\textsuperscript{31}
Fig. 8. Proposed scheme of some of the neural connections within the dorsal horn. Large primary afferent fibers of the medial division of the dorsal root entering the spinal gray matter in deep layers, ascending to terminate on large neurons of the nucleus proprius and on small neurons of the substantia gelatinosa. Small primary afferent fibers of the lateral division entering and terminating on marginal cells of layer 1.

soma of the marginal cells, forming a “feedforward” inhibitory circuit (Fig. 8).

The large primary afferent fibers make excitatory synapses on substantia gelatinosa neurons and on the large neurons of the nucleus proprius (Fig. 8). It is thought that repetitive activation of substantia gelatinosa cells by impulses from large primary afferents would result in massive inhibition of the marginal cells, the recipients of small-fiber input. This neural circuit would provide one means by which large primary afferent input could modulate pain thresholds.

It is a common experience, for example, that the pain following a cut on the finger is reduced by local pressure to nearby structures. Presumably the increased activity in large fibers reduces the transmission of small-fiber signals.

The application of a counterirritant is thought to reduce pain in a similar way. That is, the high-frequency discharge initiated by thermal receptors in response to the counterirritant reduces the transmission of small-fiber impulses and hence reduces the pain sensation.

Neurons in the spinal gray matter are thought to provide one ascending system for pain (Fig. 9). Perhaps such a system accounts for the recurrence of pain in 50 percent of the patients who undergo an anterolateral cordotomy, which interrupts the major ascending pathways.

An important concept to be derived from this analysis of the dorsal horn circuitry is that the spinal cord is not just a relay station. It is an integrative center for sensory processes. All sensory input is subjected to highly complex integrative processes whereby individual modalities are not simply channeled into rigidly determined ascending pathways.

Numerous synaptic events occur before an incoming signal reaches a second- or third-order neuron that projects to higher levels. The vast majority of ongoing dorsal root input is filtered out without ever reaching consciousness.

There is great flexibility in the system. Filtering mechanisms can be instantly suppressed. For example, all one needs to do is direct his attention to the painful area and suddenly the noxious stimulation has a “hot line” directly to higher levels. All other messages are ignored until the emergency is over or the “attention” is again distracted.

ASCENDING SYSTEMS SUBSERVING PAIN

The spinothalamic tracts convey pain impulses to the brain. The neurons of these tracts lie in laminae I and V of the dorsal horn and in the intermediate and ventral gray matter. It is not known whether there are any interconnections among these neurons. The majority of these neurons project to the contralateral side. Most of these spinal neurons respond to tactile and intense pressure stimuli as well as noxious stimuli, as if they were wide dynamic range cells.

The lateral spinothalamic tract (Fig. 3) is sometimes called the neospinothalamic division. It projects to the posterior group of the thalamic nuclei. In coursing through the brain this tract has close anatomical association with the medial lemniscus. This division of the spinothalamic system is thought to be important for the spatial and temporal discriminative aspects of pain and touch sensation.
The ventral spinothalamic tract (Fig. 3) is sometimes called the paleodivision. It projects to the medial and intralaminar nuclei of the thalamus. Because these nuclei are not organized to provide detailed somatotopic discrimination, the ventral spinothalamic tract is assumed to participate in aversive motivation and other nondiscriminative aspects of pain.

The spinothalamic fibers send out collaterals to many levels of the reticular formation in their ascent from the spinal cord.

Reticular Formation

The medullary and pontine reticular formation is a major recipient of input from the ventrolateral spinal cord and the trigeminal nucleus caudalis. Nearly all bulboreticular neurons respond to innocuous stimuli. Many show a wide dynamic range of responsiveness and most have large receptive fields. However, there are some cells that respond only to noxious stimulation. The nucleus reticularis gigantocellularis is thought to be a relay nucleus for pain in the spinoreticulothalamic system. Neurons of this nucleus are activated by noxious somatic stimuli and Aδ-fiber input. Whether these signals are important for conscious awareness of pain or for the reflex responses to pain is not known. However, the connections of the reticular formation with the hypothalamus and the limbic system suggest that the reticular formation probably plays an important role in the motivational and affective states associated with pain.

Mesencephalic reticular neurons also participate in pain mechanisms. Some, in fact, respond exclusively to noxious stimuli. Stimulation of these neurons in the experimental animal provokes aversive behavior. Destruction of these neurons reduces an animal’s response to noxious stimulation.

Projections of the reticular neurons are extensive. The bulboreticular neurons send projections 1) to the mesencephalic reticular formation and into the medial and intralaminar nuclei of the thalamus and 2) to the periaqueductal central gray matter of the midbrain. The periaqueductal central gray matter, in turn, sends projections to the surrounding mesencephalic reticular formation by way of the dorsal longitudinal fasciculus to the dorsal and posterior hypothalamus, and the midline and intralaminar groups of the thalamus.

THALAMUS

The ventral nuclear complex is the terminus for the dorsal column-medial lemniscus as well as for the spinothalamic tract in primates. In fact, the majority of the ventrobasal neurons respond exclusively to innocuous stimulation of the contralateral side of the body. Lesions in this region produce profound deficits in somatosensory discrimination, but have little effect upon pain. It appears that the ventral nuclear complex plays a less important role in pain than do other regions of the thalamus.

The posterior nuclear complex, like the ventral nuclear complex, receives input from the dorsal column nuclei. It is also the terminus for fibers from the ventrolateral quadrant of the spinal cord. Cells of the posterior nucleus respond to noxious as well as innocuous stimulation of the contralateral (and in some cases ipsilateral) regions of the body. Because of the direct spinothalamic projections to the posterior thalamic complex, it is assumed that this region is part of a specific pain pathway involved in the discriminative aspects of pain sensation.

The medial and intralaminal thalamic nuclei of the thalamus make up the generalized or diffuse system of the thalamus. They receive input from the paleospinothalamic fibers directly from the ventrolateral spinal cord and indirectly from the bulb reticular formation, especially from the nucleus gigantocellularis. The neurons of these midline nuclei respond to both nocuous and innocuous stimuli delivered to wide areas on either side of the body, but there is no somatotopic organization. Lesions in the medial and intralaminar system are effective in relieving intractable pain in man. Such lesions relieve the affective dimension of pain while preserving somatosensory discrimination. From these observations it appears that these diffuse nuclei of the thalamus are involved in the nondiscriminative aspects of pain.

CORTEX

The role of the cerebral cortex in pain has been a matter of considerable controversy, but the bulk of evidence available today suggests that the primary receiving area for somatic sensory information (the postcentral gyrus) is not essential for pain perception. Nonetheless, evoked potentials can be detected in the contralateral central area of the cortex in response to stimulation of the Aδ afferent fibers of tooth pulp. This evidence suggests that some ascending pain pathways may project to restricted regions of the cortex. Most of the posterior group of thalamic neurons project to the retroinsular cortex, a...
region not easily accessible for recording or surgical intervention.\textsuperscript{170-172}

The diffuse system of the thalamus provides heavy input to the striatum but only indirect, diffuse projections to the cortex. Hence, the cortex may play some as yet poorly defined role in pain, but it is presumed not to be an important part of a specific pain pathway.\textsuperscript{165}

**DESCENDING SYSTEMS INVOLVED IN PAIN**

A significant portion of CNS activity is directed toward the selection, modulation, and control of ascending sensory information by means of descending fibers. For comprehensive reviews see articles by Wall and Dubner,\textsuperscript{173} Lynn,\textsuperscript{174} and Fields and Basbaum.\textsuperscript{175}

Some of these descending systems are highly specific for the modulation and control of pain. The cerebral cortex, periaqueductal gray matter in the brain stem, and the serotonergic neurons of the raphe magnus nucleus are among the brain regions known to exert pronounced modulatory effects on neural transmission in the substantia gelatinosa of the dorsal horn (Fig. 10).

These descending impulses not only influence synaptic transmission from sensory fibers at the level of the first synapse in the dorsal horn of the spinal cord, but they also act at the bulbocerebellar and diencephalic levels to modulate ascending information at every level of the neuraxis. Furthermore, at every level that receives ascending sensory input, there are neurons with descending processes capable of influencing the input into that area. The functional significance of these descending pathways is becoming increasingly apparent as new knowledge about pain evolves (see Parts II and III of this review).