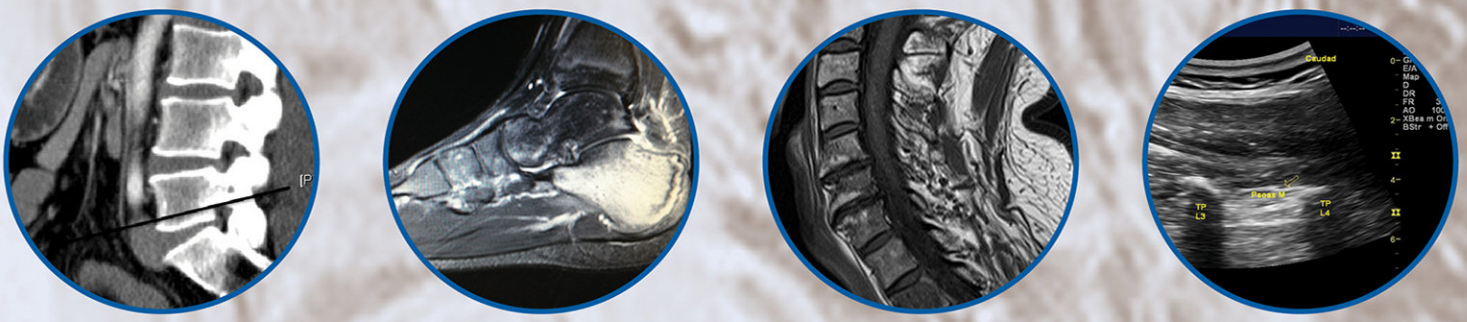
3rd edition

Principles and Practice of Pain Medicine



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Mc Graw Hill Education

Principles and Practice of Pain Medicine

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Third Edition

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This book is dedicated to my wife Fatima and children Ahmad, Tania, Sarah, and Zaydan,
"for I have learned that every heart will get what it prays for most." (Hafez).

Zahid H. Bajwa, MD

This book is dedicated to my wife Lois for her
"faith, hope, and love; and the greatest of these is love." (I Cor 13:13).

R. Joshua Wootton, MDiv, PhD

To my husband Gordon and my children Richard, Chris, and Alexandra for their love and support.

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Foreword

The alleviation of pain has been central to the humane practice of medicine since its ancient beginnings. How this essential mission has been carried out, however, has evolved exponentially with time, driven by the expansion of medical knowledge, the invention of new treatments, and ongoing changes in the practice of medicine itself. Today, this evolution is unfolding in the United States against the backdrop of radical changes in the way in which healthcare is practiced and financed.

The rapid pace of change in the knowledge and care of pain has motivated this revised and expanded third edition of *Principles and Practice of Pain Medicine.* Since the previous edition was published in 2004, new treatments and treatment modalities have been created; a major paradigm shift has occurred in the use of opioid analgesics; and substantial progress has been made in how pain is studied, taught, and treated.

What has not changed is the demand for pain relief. If anything, the tide of patients in pain has swelled: the Institute of Medicine (IOM) reported in 2011 that about 100 million American adults suffer from chronic pain, more than those suffering from diabetes, heart disease, and cancer combined.[1] The annual direct and indirect cost is estimated to exceed $600 billion annually;[1] and these estimates do not include the burdens of acute pain, pain in pediatric populations, cancer-related pain, or pain at the end of life. Opioid analgesics, which have been widely deployed in the past decade against this onslaught of chronic pain, continue to be associated with efficacy data that is weak to inadequate. In addition, these agents have proven to pose substantial risks and to require greater caution than was widely recognized prior to publication of the second edition. Since then, data have convincingly shown a trend toward the excessive prescribing of opioids, as well as the dramatic scope of the U.S. epidemic of prescription drug abuse, which only recently has shown signs of easing.[2]

Viewing the IOM findings of high prevalence and costs of pain, in the light of both the epidemic of prescription opioid abuse and the fact that the U.S. presently consumes the vast majority of the world supply of prescription opioids, strongly suggests that many patients are being inadequately treated for their pain. It has become clear that inadequate treatment may result from too *much* as well as too *little* treatment. We are reminded that the enthusiasm for the benefits of analgesic therapies must be tempered by a clear-eyed appreciation for their risks. This is just one of the important attitudinal shifts that have been reflected in the revisions of this third edition—shifts that may also apply to procedural and psychosocial options for pain management.

Currently, medicine possesses greater knowledge and more tools to manage pain than ever before. Yet the foundational scientific knowledge base for pain is still insufficient to fully support treatment decisions and major health policies. The National Institutes of Health continues to spend a disproportionately small fraction of its budget on pain relative to the substantial burden of pain on patients and society at large. In addition to inadequate funding of research in pain medicine, education about pain and its safe and effective management is astonishingly under-represented in the curricula for most pre-licensure healthcare professional schools, as well as post-graduate and continuing education programs. According to the 2011 IOM report on Pain in America: *"Despite the large role that care of patients with pain will play in their daily practice, many health professionals, especially physicians, appear underprepared for and uncomfortable with carrying out this aspect of their work. These professionals need and deserve greater knowledge and skills so they can contribute to the necessary cultural transformation in the perception and treatment of people with pain."* The transformation for pain care envisioned by the IOM will require recognizing pain and its management as a core component of the education for every health professional.

Many of the obstacles that impede progress in addressing pain may be attributed to its omnipresence throughout healthcare, which confounds division into neat partitions and units. The traditional organizations that are intended to support patient care, education, and research are often unable to fully integrate the vast dimensions of pain, too often leading to fragmented organizations and programs. It is no surprise that pain remains poorly integrated within the siloed departmental structure of traditional medicine or the vital institutions that support research and education. These systemic failings mean that clinicians (generalists *and* specialists), as well as educators, researchers, and students, are too often ill-equipped to effectively deal with the challenge of helping the millions of Americans who have complex, multi-dimensional pain conditions.

In the midst of massive economic uncertainty in U.S. healthcare, it might appear that we simply cannot afford to make such foundational changes. However, evidence of the costs associated with the current epidemic of prescription drug abuse, as well as the substantial costs associated with inadequately treated pain, suggests that we cannot afford *not* to make these changes. Doing so will require intensified partnerships and integration within our health systems and with the organizations that fund our research, accredit our schools for health professionals, and license and certify our clinicians and healthcare facilities.

It could be easy to despair in the face of these challenges. Yet the years since the previous edition of *Principles and Practice* have also witnessed many hopeful changes. Science continues its steep growth in knowledge of pain, and pain management is increasingly recognized as integral to healthcare. Both of these perspectives drive the advancement of treatment forward. Recent thoughtful policy and regulatory changes raise hope that we are in the process of reversing our excessive reliance on opioids for chronic pain, which may stem the current epidemic of prescription opioid abuse and overdose. Substantial efforts at the federal level are currently underway, holding the promise of an integrated national strategy for pain care, research, and education.

The third edition of this textbook represents over two decades of sustained commitment to interdisciplinary pain education by many thought leaders including Dr Bajwa, Dr Wootton, and Dr Warfield. With its many revisions and updates, this volume presents a review of current perspectives that will be invaluable to specialists and generalists across many health professions. The principles and practice of pain medicine will continue to evolve, of course, but the authors of future editions may look back on this edition as reflecting an important time in medical history. Perhaps they will see that we were at a tipping point beyond which pain care would be solidly founded on quality evidence, comprehensive education, and integration throughout healthcare.

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[1]Institute of Medicine. *Relieving pain in American: a blueprint for transforming prevention, care, education, and research*. June 2011.
[2]Centers for Disease Control and Prevention. National Vital Statistics Report: Deaths: Final Data for 2013.

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Preface

Dr Carol A. Warfield published the first edition of this book in 1992 as *Principles and Practice of Pain Management* with 39 chapters. At around the same time, the Accreditation Council for Graduate Medical Education (ACGME) began the process of formally accrediting pain medicine fellowship training programs. The majority of ACGME-accredited pain programs were based in anesthesia departments, but within a few years, physicians from other specialties were welcomed into inter-disciplinary pain fellowship programs. The International Association for the Study of Pain (IASP) was soon joined by many other professional pain societies with the mission of bringing clinicians and researchers to think and work together to understand pain and help find better treatments for patients in pain.

From the "decade of the brain" to the "decade of pain control and research," our improved understanding of pain mechanisms led to more and generally better treatments for our patients. The second edition of this book, published in 2004, was a larger and more comprehensive text reflecting those advances and was entitled *Principles and Practice of Pain Medicine.* Not only had it expanded to 87 chapters, including emphasis on headache disorders, cancer pain, and palliative medicine, but it had also enhanced the multidisciplinary collaborative spirit among editors and authors. Since the publication of the second edition of *Principles and Practice of Pain Medicine,* the field of pain medicine has matured even further as a multidisciplinary specialty with a broad scientific and clinical knowledge base. This third edition seeks to capture the essentials of this knowledge and understanding in a comprehensive review of pain medicine. Since the topic of analgesia is the domain of no single discipline, the content of this book is authored by leaders who represent the many disciplines that constitute this evolving field. One could easily write entire volumes about the topics of each of the chapters in this text, but the task of the authors and editors here was to assimilate this large body of information on pain medicine and condense it into a useful textbook of manageable size. Each chapter represents a careful distillation of current science, key concepts, and clinical treatments of the subject at hand into an accessible format. For those readers seeking to expand their horizons further, the authors have prepared extensive lists of references at the end of each chapter to provide the reader with further details.

This third edition discusses the fundamental dimensions of pain, the various disorders in which pain poses a major problem, and the methods employed in its management, with special emphasis on the use of injections and nerve blocks as an aid to diagnosis, prognosis, and therapy. It covers the biology of pain and the principles of physical and psychological evaluation of chronic pain. It goes on to discuss pain categorized by anatomic location, as well as by syndrome, such as acute and peri-operative pain, neuropathic pain, pain in the terminally ill, and pediatric and geriatric pain. The authors have been careful to incorporate vivid illustrations depicting the physical symptoms and anatomy of each site, as well as key findings from MRI, CT, X-rays, and other imaging and diagnostic technology. The next group of chapters discusses pain therapies and includes detailed attention to pharmacologic treatments, interventional therapies, and complementary and physical treatments of pain. Lastly, because pain medicine has now grown beyond its clinical bounds, we have introduced chapters covering the new areas of pain and law, ethics, and business administration.

The breadth and rapidity of change in this specialty has prompted the publication of this edition, reflecting the expansion of pain medicine with former chapters updated and new chapters added. We have also attempted to be comprehensive in our consideration of pain medicine from a multidisciplinary perspective, with the idea that, regardless of the reader's background and training—whether anesthesiology, medicine, neurology, physical medicine and rehabilitation, neurosurgery, psychology, or other specialties—a picture of pain medicine as a multifaceted and continually evolving field emerges.

We extend our thanks to all of the chapter authors for their tireless work on this project and extend a special thanks to Dr Scott M. Fishman for writing the foreword to the third edition of this textbook and to Drs Thomas T. Simopoulos and John Keel for their help in developing content and multiple contributions. We welcome comments, suggestions, and constructive criticism from all our readers.

Zahid H. Bajwa, MD
R. Joshua Wootton, MDiv, PhD
Carol A. Warfield, MD

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PART 1

Pain: Biology, Anatomy, and Physiology

CHAPTER 1

Molecular Biology of Pain

Tony L. Yaksh

"Stimuli become adequate as excitants of pain when they are of such intensity as threatens damage to the skin."

—Sherrington (1906)[1]

OVERVIEW

The acute activation of small sensory afferent axons by high-intensity thermal and mechanical stimuli evokes locally organized spinal motor reflexes (nociceptive reflexes), autonomic responses, and pain behavior in animals and humans. This effect is mediated by the local encoding of afferent input at the level of the dorsal horn and the activation of spinofugal projection neurons. These projection systems travel both ipsilaterally and contralaterally in the ventrolateral aspect of the spinal cord, projecting supraspinally into the medulla, mesencephalon, and diencephalon. Medullary projections serve to activate spinobulbospinal reflexes that influence autonomic tone. Other projections into the mesencephalon and thalamus are assumed to contribute to the perceptual and complex emotive and discriminative components of the pain state. It is important to appreciate that encoding by the sensory afferent and the spinal dorsal horn of the nociceptive stimulus is the first step in nociceptive processing, and this encoding process contributes properties that are important to the understanding of the behavioral correlates of nociception. The following sections consider aspects of the mechanisms whereby injury leads to an ongoing pain state from the perspective of the organization of the sensory afferents and the spinal dorsal horn. Of particular importance is the appreciation that these linkages have distinct pharmacologies and that these systems can be regulated to display prominent increases (hyperalgesia) and decreases (analgesia) in the input–output function.

PRIMARY AFFERENTS

MORPHOLOGY

Sensory afferents represent the first link between the nervous system and the peripheral milieu. Whether they are enteroceptive organs such as viscera or blood vessels, the meninges, deep structures such as muscle or joint, or the skin, all surfaces are innervated by axons that transduce the local milieu to generate action potentials that provide input to the neuraxis. These primary afferent axons are made up of the central (root) and peripheral (nerve) projections and the dorsal root ganglion cell body that is connected to the root by a sinuous glomerulus. With the exception of several cranial nerves, all axons have their primary cell body in the dorsal root ganglia that lie outside of the neuraxis proper.[2]

NORMAL SENSORY AFFERENT ACTIVITY

Classification of Sensory Afferents These axons may be classified according to the nature of the peripheral terminals, their size (large or small), and state of myelination (myelinated or unmyelinated), as well as, functionally, their conduction velocity (large axons are rapid; small axons are slower) and the modality of stimulation that most effectively results in activity in the associated axon.

Sensory Nerve Endings It is important to emphasize that the peripheral afferent terminal is an exceedingly specialized region. The terminal provides the transduction properties that convert stimulus of a given modality into a local sodium channel–mediated depolarization that leads to activity in the afferent axon.[3] This degree of depolarization leads to activation of the axon, the frequency of which is proportional to the stimulus intensity. Large axons typically display complex, specialized structures, such as pacinian corpuscles or stretch sensitive organs, that transduce mechanical stimuli and define the nature of the afferent response—for example, a rapidly adapting response in which a continued stimulus may evoke an output when the stimulus is applied and then again when it is removed (i.e., rapidly adapting, as compared with slowly adapting). Small afferents may not display evident specialization and, hence, are commonly referred to as being "free" nerve endings. These free nerve endings are, however, extremely complex, providing a transduction of different modalities and various chemical stimuli.[4]

TABLE 1-1 Primary Afferents Classed by Conduction Velocity and Physical Nature of the Effectivew Stimulus

Fiber Class[a]	Velocity	Effective Stimuli
Aβ (myelinated) (12–20 μ dia)	Group II (>40–50 m/sec)	Low-threshold mechanoreceptors
		Specialized nerve endings (pacinian corpuscles)
Aδ (myelinated) (1–4 μ dia)	Group III (10< × <40 m/sec)	Low-threshold mechanical or thermal
		High-threshold mechanical or thermal
		Specialized nerve endings
C (unmyelinated) (0.5–1.5 μ dia)	Group IV (<2 msec)	High threshold thermal, mechanical, and chemical
		Free nerve endings

[a]Aβ/Aδ/C is the Erlanger-Gasser classification and refers to axon size; II/III/IV is the Lloyd-Hunt classification and is defined on conduction velocity in muscle afferents. Because of the relationship between size and state of myelination with conduction velocity, these designations are often used interchangeably.

Effective Stimuli Under normal conditions, the cardinal observation is that sensory afferents show minimal, if any, spontaneous activity. However, the brief application of a peripheral mechanical or thermal stimulus will often evoke intensity-dependent increases in firing rates. As outlined in **Table 1-1**, recording from fibers identified according to their conduction velocity reveals that large Aβ (group II) fibers are typically activated by low thresholds (i.e., mechanoreceptors). Small, lightly myelinated axons Aϑ (group III) fibers that conduct at a lower velocity may belong to populations that are heterogeneous, responding to low or high thresholds, mechanical or thermal. Thus, low-threshold afferents may begin firing at temperatures that are not noxious (30°C) and increase their firing rate monotonically as the temperature rises. Other populations of Aϑ fibers may begin to fire at temperatures that are mildly noxious and increase their firing rates up to very high temperatures (52–55°C). These would be referred to as thermal nociceptors. Small, unmyelinated, slowly conducting afferents (C fiber or group IV) constitute the largest population of sensory axons. The large majority of these small afferents are activated by high-threshold thermal, mechanical, and chemical stimuli and are, therefore, called C-polymodal nociceptors.[5] Accordingly, the afferent input from a given stimulus will reflect on (1) the modality of the stimulus (e.g., thermal, mechanical, or chemical) and (2) the coactivation of several populations of afferents, which transduce that stimulus energy and a discharge frequency that covaries with stimulus intensity over a range reflecting a low versus high stimulus-intensity threshold (**Fig. 1-1**).

Psychophysical Correlates of Afferent Activity In normal, uninjured tissue, stimuli that give rise to activity in small sensory afferents evoke a psychophysical report of pain sensation in humans and a somatotopically organized escape response in animals (e.g., withdrawal of the stimulated limb). The intensity of the report and the vigor of the escape are typically monotonically correlated with stimulus intensity and, hence, with the frequency of discharge in a given sensory axon. Conversely, electrical activation of Aδ nociceptors produces a short-lasting pricking sensation (first pain), whereas activation of C fibers results in a poorly localized burning sensation (second pain). In the absence of tissue injury, the removal of the stimulus leads to rapid abatement of the afferent input and disappearance of the pain sensation.

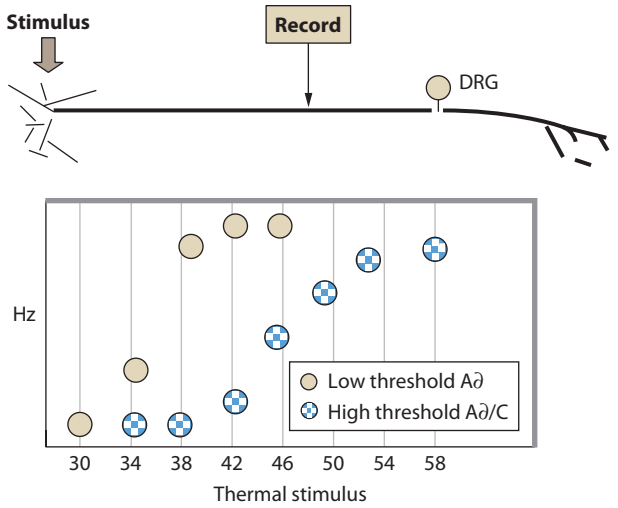

FIGURE 1-1. (**Top**) Schematic of sensory axon fiber with peripheral nerve ending. (**Bottom**) Two types of fibers—low-threshold Aϑ and high-threshold Aϑ and C fibers—typically show little, if any, spontaneous activity but show a monotonic increase in response to increasing stimulus intensities. For the high-threshold afferents, the triggering threshold usually reflects temperatures that would correspond to a temperature at which a pain report would be elicited.

AFFERENT ACTIVITY AFTER TISSUE INJURY

Afferent Response After Tissue Injury If a stimulus produces a local injury, as in a tissue crush or incision, two events are observed to occur.

1. The normally silent sensory afferent begins to display a persistent bursting discharge that continues for an extended interval (minutes to hours) after the injuring stimulus is removed (**Fig. 1-2**).
2. The stimulus intensity required for activating the otherwise high-threshold afferent may fall significantly, such that otherwise moderately intense stimuli will be highly effective. In effect, this serves to shift the relationship between response (frequency of discharge) and stimulus intensity up, to the left, and increases its slope. The extreme example of this peripheral sensitization is the population of afferent C fibers referred to as silent nociceptors. These afferents are normally only poorly activated by even extreme mechanical stimuli. In the presence of tissue injury or inflammation, these previously silent afferents may develop spontaneous activity and a low mechanical threshold.

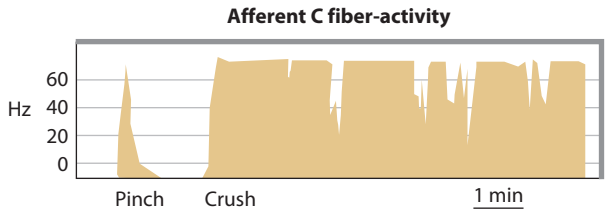

FIGURE 1-2. Schematic presenting the firing rate to pinch and to tissue crush of a single, small, cutaneous afferent axon. Note that in the absence of stimulation, there is no spontaneous activity in this small afferent axon. After a brief pinch, there is a brief stimulus-linked discharge. Creation of tissue injury by a mechanical crush leads to a prolonged, ongoing discharge.

Origin of Persistent Afferent Activity The ongoing activity observed after injury originates from the terminal region of the sensory afferent and appears to have two sources:

1. Afferent terminals that are in the vicinity of the injury may develop spontaneous activity, in part because of local damage to the terminal that may result in an increase in local sodium channel activation.
2. A tissue-injuring stimulus will lead to the release of local factors that (a) directly activate the local terminals of afferents (that are otherwise silent), and (b) facilitate the discharge of the afferent in response to otherwise submaximal stimuli (**Fig. 1-3**). Some of these local factors are enumerated in **Table 1-2**. Importantly, exogenous administration of these products has been shown to directly excite

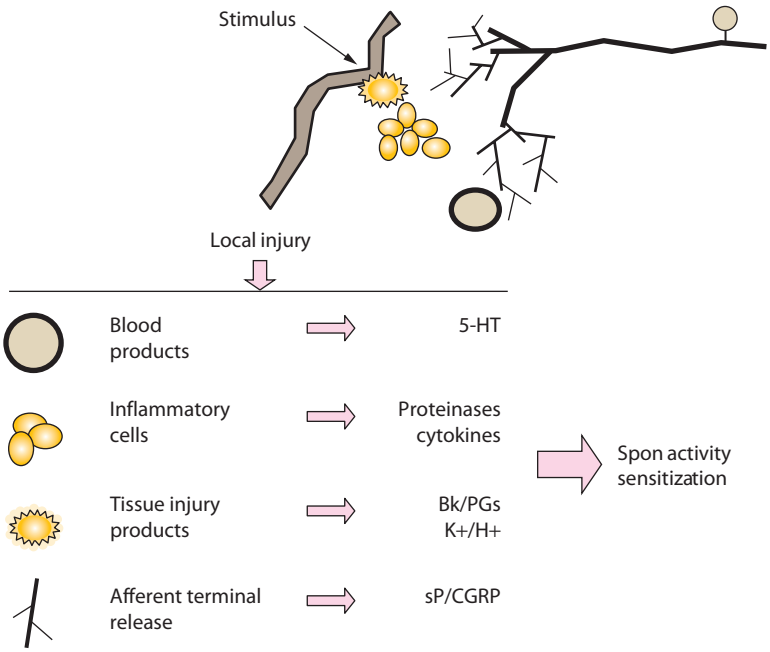

FIGURE 1-3. Schematic of local organization causing changes in the chemical milieu in the region of a local injury that lead to afferent activation and sensitization. Primary afferent terminal A: Local damaging stimulus leads to activation of the fine sensory afferent (C fiber). Activity proceeds orthodromically to the spinal cord and antidromically to invade local peripheral collaterals. This antidromic activity can depolarize the peripheral terminals and locally release their peptide content. The orthodromic traffic reaches the spinal cord and may serve to produce sufficient local depolarization in the dorsal horn that an antidromic action potential is generated in the terminals of an adjacent sensory axon. The antidromic activity generated by a local axon reflex and by the spinal component invades the distal terminal region locally to release neuropeptides (substance P [sP], calcitonin gene–related peptide [CGRP]). Local injury and the released hormones serve to activate local inflammatory cells. Hormones, such as bradykinin, prostaglandins, and cytokines, or K^+/H^+ released from inflammatory cells and plasma extravasation products result in stimulation and sensitization of free nerve endings.

TABLE 1-2 Classes of Agents Released After Tissue Injury That Influence Activity in Small Primary Afferent Fibers[a]

Agents	Action
Amines	Histamine (granules of mast cells, basophils, and platelets) and serotonin (mast cells and platelets) are released by a variety of stimuli, including mechanical trauma, heat, radiation, certain byproducts of tissue damage, thrombin, collagen, epinephrine, and members of the arachidonic acid cascade, leukotrienes, and prostanoids.
Kinin	A variety of kinins, notably bradykinin, are released by physical trauma. Peptide is synthesized by a cascade that is triggered by the activation of factor XII by agents such as kallikrein and trypsin. Bradykinin acts by specific bradykinin receptors (B1/B2) to activate free nerve endings.
Lipid acids	Agents are synthesized by lipoxygenase or cyclooxygenase (prostanoids) upon the release of cell membrane–derived arachidonic acid secondary to the activation of phospholipase A_2. A number of prostanoids, including PGE_2, can directly activate C fibers. Others such as PGI_2 and TXA_2, and several leukotrienes, can markedly facilitate the excitability of C fibers. These effects are also mediated by specific membrane receptors.
Cytokines	Cytokines such as the interleukins are formed as part of the inflammatory reaction involving macrophages and have been shown to exert powerful sensitizing effects on C fibers. Interleukins such as Il-1 may sensitive C fibers via a prostaglandin intermediary.
Primary afferent peptides	CGRP and sP are found in and released from the peripheral terminals of C fibers and will produce local cutaneous vasodilation, plasma extravasation, and sensitization in the region of skin innervated by the stimulated sensory nerve.
[H]/[K]	Elevated H^+ (low pH) and high K^+ are found in injured tissue. These ions can directly stimulate C fibers and facilitate the discharge produced by a given stimulus (e.g., hyperalgesia activates the local axon reflex and results in the local release of CGRP, a potent vasodilator and modulator of plasma extravasation). A population of C nociceptors sensitive to noxious intensities of mechanical and thermal stimuli also responds in a stimulus-released fashion to solutions of increasing proton concentration injected into their receptive fields. These receptors develop a lower threshold and enhanced response to mechanical stimuli. Similar injections in humans induce a sustained graded pain and hyperalgesia. Increasing evidence suggests that agents such as capsaicin may interact directly with peripheral terminal membranes to increase proton conductance.
Proteinases	Thrombin or trypsin, among others, are released from inflammatory cells and can cleave tethered peptide ligands that exist on the surface of small primary afferents. These tethered peptide act upon adjacent receptors (PARs) that can serve to depolarize the terminal, causing an orthodromic input and the local release of sP and CGRP into the injured tissues.

[a]CGRP, calcitonin gene–related peptide; PAR, proteinase-activated receptor; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2; sP, substance P; TXA_2, thromboxane A_2.[6-8]

C fibers and facilitate C-fiber firing, resulting in a shift to the left and increased slope of its frequency response curve.[6] For the substances in which it has been examined, these agents, when applied to the skin of humans and animals, usually evoke pain behavior and increase the magnitude of the reported pain response evoked by a given stimulus (hyperalgesia) (**Fig. 1-4**).[7,8]

In short, peripheral mechanical and thermal stimuli will evoke intensity-dependent increases in firing rates of small afferents, and this response corresponds to the psychophysical report of pain sensation in humans and the vigor of the escape response in animals. Such stimuli may result in local injury and the subsequent elaboration of active products that directly activate the local terminals of afferents (which are otherwise essentially silent) innervating the injury region and facilitate their discharge in response to otherwise submaximal stimuli.

SPINAL SYSTEMS ENCODING SENSORY INPUT EVOKED BY INJURY

Sensory afferents project into the spinal dorsal horn and make synaptic contact with dorsal horn neurons. Two issues pertinent to our understanding of spinal organization should be considered: (1) the organization of the afferent termination in the dorsal horn and (2) the classes of neurons that receive these projections.

GENERAL ORGANIZATION OF THE SPINAL DORSAL HORN

The spinal cord is divided into several broad anatomic regions (dorsal root entry zone, dorsal horn, and ventral horn; gray and white matter). These regions are further divided on the basis of descriptive anatomy into spinal lamina (Rexed)[9,10] (**Fig. 1-5**).

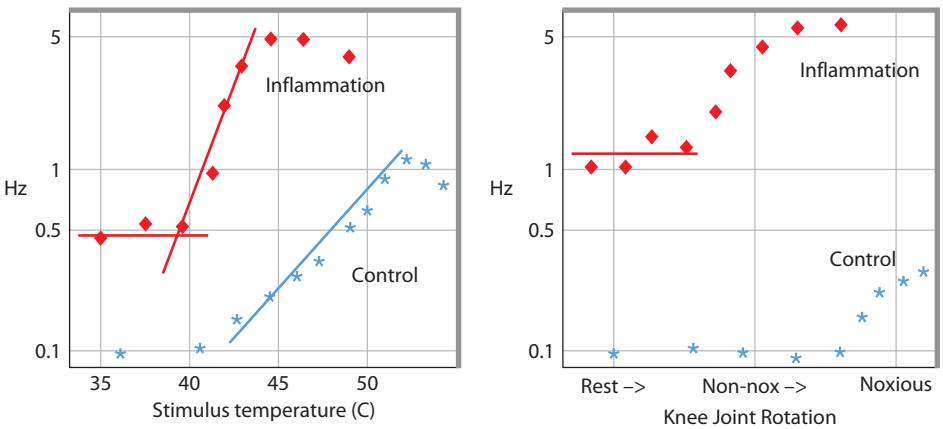

FIGURE 1-4. Representation of the response of small axons innervating the skin to thermal stimuli before and after the injection of a local inflammatory substance (**left**) and the activity in an afferent to a range of knee joint motion before and after inflammation of the knee joint (**right**). Following the initiation of cutaneous inflammation, the afferent shows increasing spontaneous activity, a left shift, and an increase in the slope in the stimulus-response curve, indicating a facilitated response to the thermal stimulus. In the knee, the articular afferent shows little response to normal rotation and only fires in response to extreme rotation. After the initiation of joint inflammation, even mild rotation results in a significant discharge.

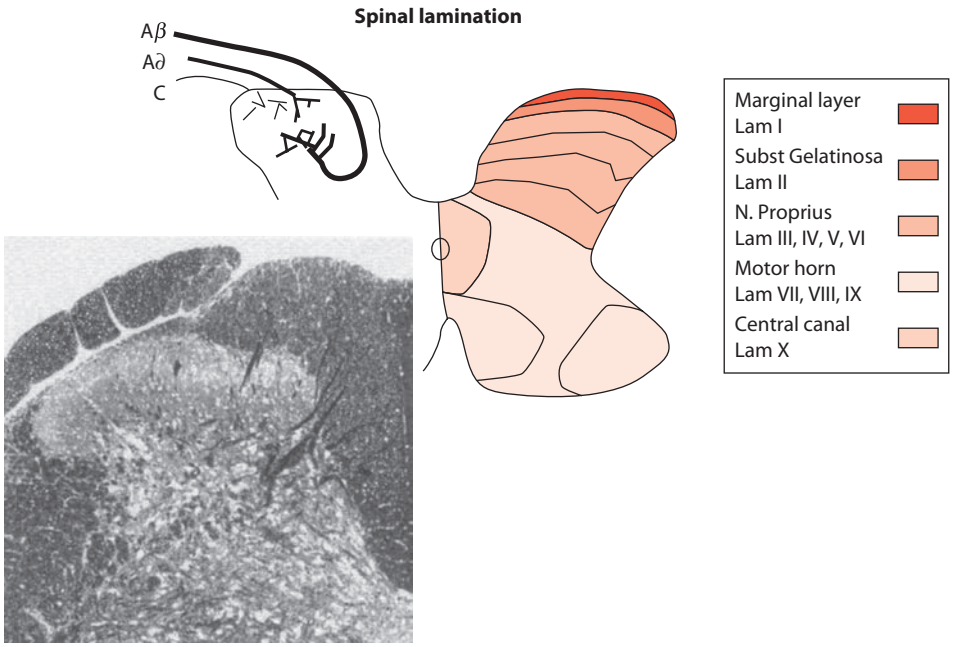

FIGURE 1-5. Schematic showing the Rexed lamination (**right**) and the approximate organization of the approach of the afferent to the spinal cord (**left**) as they enter at the dorsal root entry zone and then penetrate into the dorsal horn to terminate in laminae I and II (A/C) or penetrate more deeply to loop upward to terminate as high as the dorsum of lamina III (Aβ). Inset in lower left shows histologic appearance of the left dorsal quadrant. Note root entry zone, substantia gelatinosa, and large, myelinated axons.

SPINAL TERMINALS OF PRIMARY AFFERENTS

Spinal Trajectory of Afferent Axons In the peripheral nerve, afferents are anatomically intermixed. As the sensory root approaches the spinal dorsal root entry zone, large afferents tend to move medially, and these displace smaller, unmyelinated afferents laterally. Upon entering the spinal cord at the dorsal root entry zone, the central processes of the afferents collateralize, sending fibers rostrally and caudally up to several segments in Lissauer's tract (small, C-fiber afferents) or in the dorsal columns (large afferents) and into the segment of entry. Upon penetrating into the parenchyma, the terminal fields ramify rostrally and caudally for several millimeters[10] (**Fig. 1-6**).

Spinal Terminals of Afferent Axons In the spinal cord, terminals from the large, myelinated afferents are found in the deeper laminae (Rexed III–VI). Smaller myelinated fibers terminate in the marginal zone (Rexed lamina I), the ventral portion of lamina II, and throughout lamina III. Small-diameter, unmyelinated fibers (C fibers) largely terminate throughout lamina II and in lamina X around the central canal.

From a functional standpoint, this ramification emphasizes that neurons that lie distal to the segment of entry of the afferent will receive excitatory input. Electrophysiologic studies have shown that whereas the strongest excitation is observed in neurons in the segment of entry, excitation from the L5 root may be observed in cells as far as five to seven segments rostrally. As discussed later in this chapter, factors that alter

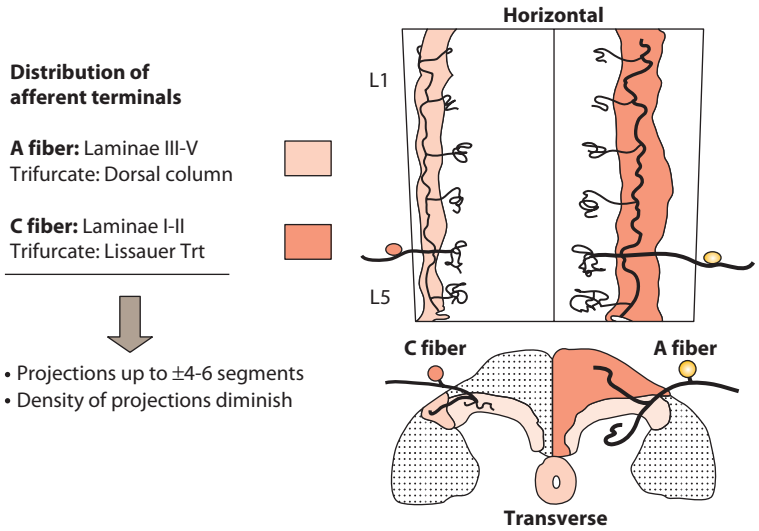

FIGURE 1-6. Schematic displaying the ramification of C fibers (**left**) into the dorsal horn and collateralization into Lissauer's tract and of Aβ fibers (**right**) into the dorsal columns and into the dorsal horn. Note that the densest terminations are within the segment of entry and that there are less-dense collateralizations into the dorsal horns at the more distal spinal segments. This density of collateralization corresponds to the potency of the excitatory drive into these distal segments.

TABLE 1-3 Summary of Several Products Contained and Released from Small Primary Afferents

Peptides	Excitatory Amino Acids	Other
Substance P	Glutamate	Purines (ATP)
Calcitonin gene–related peptide	Aspartate	
Galanin		
Vasoactive intestinal polypeptide		
Somatostatin		

ATP, adenosine triphosphate.

the excitability of these distant neurons may thus increase the apparent size of the receptive field for a given neuron.[11,12]

PRIMARY AFFERENT TRANSMITTERS

Activation of primary afferents typically induces a postsynaptic excitation. Excitation is mediated by the release of neurotransmitters from the afferent terminal. Considerable effort has been directed at establishing the identity of the excitatory neurotransmitters in the primary afferent. Some of these are listed in **Table 1-3**.[13]

Characteristics of Primary Afferent Transmitters A number of properties characterize the transmitters that are contained in and released from the primary afferent. Peptides and glutamate have been shown to exist within subpopulations of small, type B dorsal root ganglion cells (giving rise to C fibers) and are in laminae I and II of the dorsal horn of the spinal cord, where the majority of primary afferent terminals are found (**Fig. 1-7**). These levels in the dorsal horn are reduced by rhizotomy or ganglionectomy, or both, or by treatment with the small afferent neurotoxin, capsaicin.

Many peptides present in large, dense core vesicles (e.g., substance P and calcitonin gene–related peptide) as well as excitatory amino acids in small, clear core synaptic vesicles (glutamate) are present in and released from the same terminal. Iontophoretic application onto the dorsal horn of the several amino acids and peptides found in primary afferents has been shown to produce excitatory effects. Amino acids produce a very rapid, short-lasting depolarization. Peptides produce a delayed and long-lasting depolarization. Local spinal administration of several agents, such as substance P and glutamate, does yield pain behavior, suggesting their possible role as transmitters in the pain process.[14]

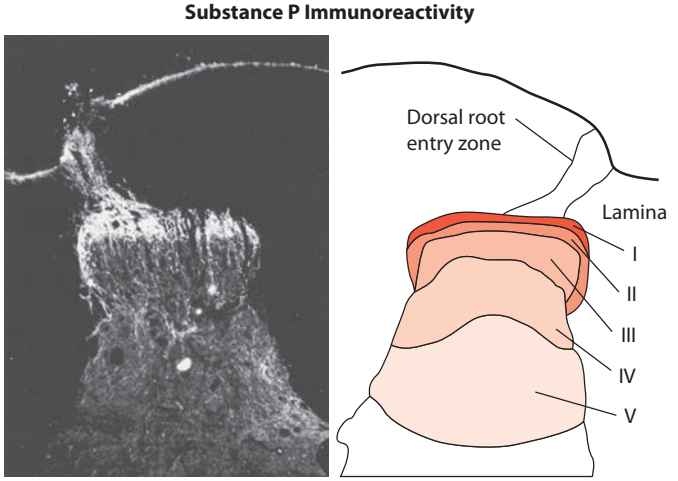

FIGURE 1-7. Histochemistry showing distribution of substance P immunoreactivity in laminae I and II (substantia gelatinosa) of the dorsal horn.

A large proportion of nociceptive dorsal horn neurons are contacted by substance P–containing terminals. Administration of noxious, but not innocuous, stimulation to the tissue results in release of several of these peptides into the spinal dorsal horn. With regard to the excitatory amino acids, their release has been evoked by acute and chronic nociceptive stimuli, including joint inflammation. Unlike the peptides, amino acids are also present in large primary afferents, and their spinal release can also be induced by activation of Aβ fibers.

CLASSES OF DORSAL HORN NEURONS

Anatomically, dorsal horn neurons may be broadly described in terms of their location (marginal layer, substantia gelatinosa, and the nucleus proprius), size (small, magnocellular), and functional response properties and neurochemistry. The complexity of this region accordingly cannot be overstated. For practical purposes related to nociceptive processing, it is reasonable to consider the functional properties of two principal classes of neurons. Electrophysiologic recording from single neurons in the spinal dorsal horn reveals several populations that are activated by high-intensity stimuli: nociceptive specific (marginal cells) and wide dynamic range (lamina V neurons) (**Fig. 1-8**).

Nociceptive-specific Neurons Marginal neurons, located in lamina I of the dorsal horn, are large neurons that are oriented transversely across the cap of the dorsal gray matter and receive input from small unmyelinated and lightly myelinated afferents (see Fig. 1-5). Some project to the thalamus via ipsilateral and contralateral ascending pathways, and others project intra- and intersegmentally along the dorsal and dorsolateral white matter. Populations of these neurons respond selectively to intense cutaneous and muscle stimulation. Whereas some are modality specific (e.g., firing in response only to thermal or mechanical stimuli), others respond to both types of stimuli. Activity in these subpopulations of neurons provides an unambiguous message that nociceptors have activated. Other prominent cell types in lamina I include (1) thermoreceptive "cool" cells that are activated and inhibited by innocuous cooling and warming, respectively, and (2) heat, pinch, and cold cells that are similar to traditional marginal cells but also are excited by noxious cold.[15]

Wide-dynamic-range (WDR) Neurons The cell bodies of lamina V cells are located in the nucleus proprius of the dorsal horn and send their apical dendrites up into laminae II and III (see Fig. 1-8). An important property of these cells is that they receive convergent input from a variety of functionally distinct primary afferents.[16] Practically, these cells demonstrate three kinds of convergence.

1. *Fiber response properties.* As indicated schematically in Figure 1-8, WDR-type cells receive input both from large, typically low-threshold afferents that project deep into the dorsal horn and from small, typically high-threshold afferents that project only into laminae I and II. As suggested schematically, some of this input, particularly that which is superficial, is mediated by excitatory interneurons. These WDR cells accordingly display a graded increase in the frequency of response to stimuli that are progressively more intense and recruit increasingly higher threshold populations of afferents Aβ to A∂ and C. This convergence thus permits these single cells to integrate input activated by a wide range of stimuli that vary in intensity, with higher frequency firing being noted as stimulus intensity rises.
2. *Spatial convergence.* As outlined earlier in Figure 1-6, primary afferents entering a specific segment have their primary excitatory input on dorsal horn neurons in that segment of entry. Still, it is clear that such axons can collateralize and mediate an excitatory effect on cells that lie in distal dermatomes. Accordingly, the size of the dermatome of that segment is actually larger than the peripheral distribution of the afferents in the root of that respective segment. As noted later in this discussion, it is likely that the size of the receptive field of a given neuron may be increased by conditions that lead to an enhancement of its excitability as inputs that are relatively weak become able to drive activity in that now-"sensitized" spinal neuron.

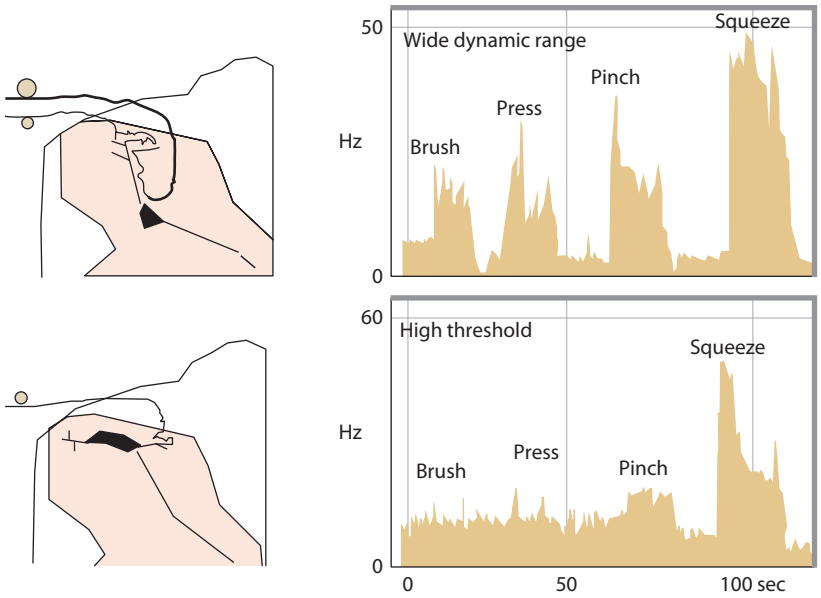

FIGURE 1-8. Schematic representing the morphology and dendritic pattern (**left**) of a lamina V, wide-dynamic-range neuron (**top**) and a lamina I, marginal neuron (**bottom**). The firing patterns of the respective classes of neurons are indicated in the representation on the right, in which a poststimulus time histogram shows the frequency of firing in response to four graded, mechanical stimuli ranging from innocuous (brush/press) to noxious (pinch/squeeze).

3. *Organ convergence.* Depending on the spinal level, a WDR neuron can be activated by input traveling with the sympathetics (e.g., as activated by distention of hollow viscera [bladder, small intestine, and gallbladder]), injection of bradykinin into the mesenteric artery, close intraarterial administration of bradykinin or the injection of hypertonic saline into muscle/tendon, or group III afferent stimulation from the gastrocnemius. The same WDR neuron can thus be excited by cutaneous or deep (muscle and joint) input applied within the dermatome that coincides with the segmental location of these spinal cells. Thus, stimulation of the skin and muscles of the left shoulder and upper arm (T_1–T_5 dermatome) activates WDR neurons that are also excited by coronary artery occlusion. These results indicate that the phenomenon of *referred* visceral pain, for example, has its substrate in the anatomic convergence of input from viscera, muscle, and skin onto the same populations of dorsal horn neurons.[17] Migraine is another example of such organ convergence. The migraine pain referred to the head arises from activation of dural afferents that project to neurons in the nucleus caudalis which receive input from afferents arising from homologous extracranial tissues. Accordingly, the migraine pain is referred to those extracranial regions.

ASCENDING SPINAL TRACTS

Clinical experience based on local spinal lesions of the ventrolateral quadrant suggests that pain is a "crossed" pathway with relevant projections traveling in the contralateral ventrolateral white matter. Midline myelotomies that destroy fibers crossing the midline at the levels of the cut produce bilateral pain deficits. These observations suggest that the relevant pathways for nociception are predominantly crossed. Similarly, stimulation of the ventrolateral tracts in awake subjects undergoing percutaneous cordotomies results in reports of contralateral warmth and pain. In accord with these observations, tract-tracing studies and electrophysiologic investigations emphasize that activity evoked in the spinal cord by high-threshold stimuli reaches supraspinal sites by several long and tract systems that travel within the ventrolateral quadrant[18] (**Fig. 1-9**).

Spinoreticular Fibers Spinoreticular axons originating in laminae V through VIII terminate ipsilaterally and contralaterally to their spinal site or origin. In the medulla, the fibers aggregate laterally, and collaterals of these fibers terminate in the more medially situated brainstem reticular nuclei. Reticulothalamic afferents excited by this input then project to the thalamus.

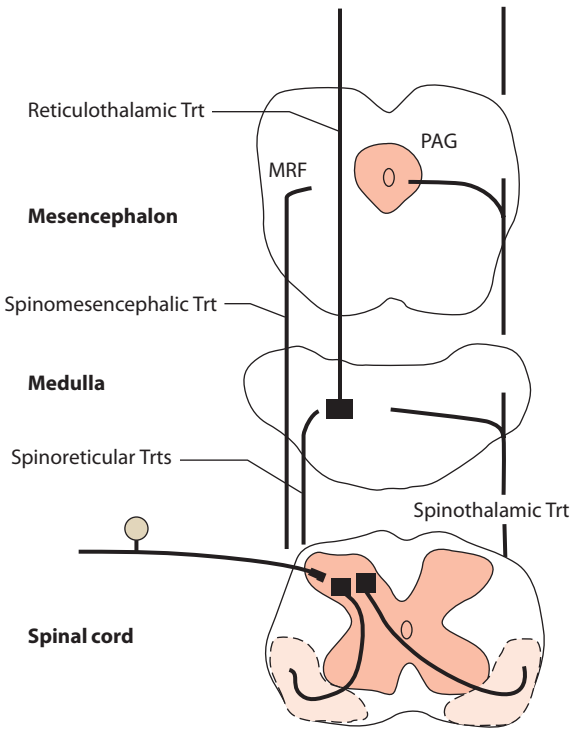

FIGURE 1-9. Schematic demonstrating the ascending crossed projections from dorsal horn neurons into the brainstem (spinoreticular) and into the thalamus (spinothalamic). The ventrobasal thalamus receives somatically mapped input from the spinal cord and projects this input into the somatosensory cortex, where the somatotopy is preserved. Other projections go to the medial thalamus and, from there, to a variety of limbic forebrain sites.

Spinomesencephalic Fibers Spinomesencephalic tracts originate primarily in lamina I, with a smaller component from laminae VI through VIII and X. They project into the mesencephalic reticular formation and the lateral periaqueductal gray matter.

Spinothalamic Fibers The cells of origin of this tract, the most extensively studied of the ventrolateral tract systems, are not limited to the dorsal gray matter, but are found throughout laminae I through VII and X of the spinal gray matter. Axons originating in the marginal layer and the neck of the nucleus proprius ascend predominantly in the contralateral ventral quadrant. Spinothalamic axons differentiate into a lateral and medial component in the posterior portion of the thalamus: The medial component passes through the internal medullary lamina to terminate in the nucleus parafascicularis and in the intralaminar and paralaminar nuclei. The majority of fibers pass laterally to terminate throughout the nucleus ventralis posterolateralis, the medial aspect of the posterior nucleus complex, and the intralaminar nuclei. A significant proportion of the neurons projecting laterally in the thalamus (ventral posterior lateral complex) also project to the medial thalamic regions such as the VMpo (ventromedial pars oralis) and Mediodorsalis portion (**Fig. 1-10**).

Suprathalamic Projection Projections to higher centers include specific mapping of input from the ventrobasal complex into the somatosensory cortex and multiple outputs particularly from the medial (VMpo/Mediodorsalis) and intralaminar nuclei projects diffusely to wide areas of the cerebral cortex, including the frontal, parietal, and limbic regions. Positron emission tomographic (PET) scanning studies in humans have confirmed that noxious stimuli will activate the appropriate cortical regions in the somatosensory cortex and limbic forebrain regions such as the insula and anterior cingulate gyrus[19] (see Fig. 1-10).

SIGNIFICANCE OF ASCENDING PATHWAYS: SENSORY-DISCRIMINATIVE AND AFFECTIVE-MOTIVATIONAL

Early thinking made the useful conjecture that pain could be considered in terms of two principal components: the sensory-discriminative and the affective-motivational components.[20] An important question is whether this functional distinction finds parallels in the underlying physiology and connectivity of the substrates thus far examined as being relevant to nociceptive processing.

At present, it is appreciated that the WDR neurons typically project into the ventrobasal thalamus, where their input is mapped precisely onto a sensory homunculus. These cells then project rostrally to the somatosensory cortex, where that input is similarly mapped onto a sensory homunculus.

In this system, each site on the body surface is faithfully mapped, and this map is maintained to the cortex. This system is uniquely able to preserve anatomic information and information regarding the intensity of the stimulus (as initially provided by the frequency response characteristics of the WDR neuron). This system is able to provide the information necessary for mapping the *sensory-discriminative* dimension of pain.

On the other hand, it has become evident that marginal, nociceptive-specific neurons also project contralaterally into the thalamus. This input thus provides one aspect of a circuit that appears to be activated by only particularly intense stimuli. This input function is defined by the response properties of the spinal marginal cell. It might be speculated that this circuit may underlie the *affective-motivational* component of the pain pathway.

The preceding recitation of the pathways through which afferent information evoked by high-threshold information travels reflects what traditionally is known as the pain pathway. In fact, this schematic, although correct, vastly oversimplifies the true organization. At every synapse, the transmission through the dorsal horn and brainstem is subject to significant modulation.

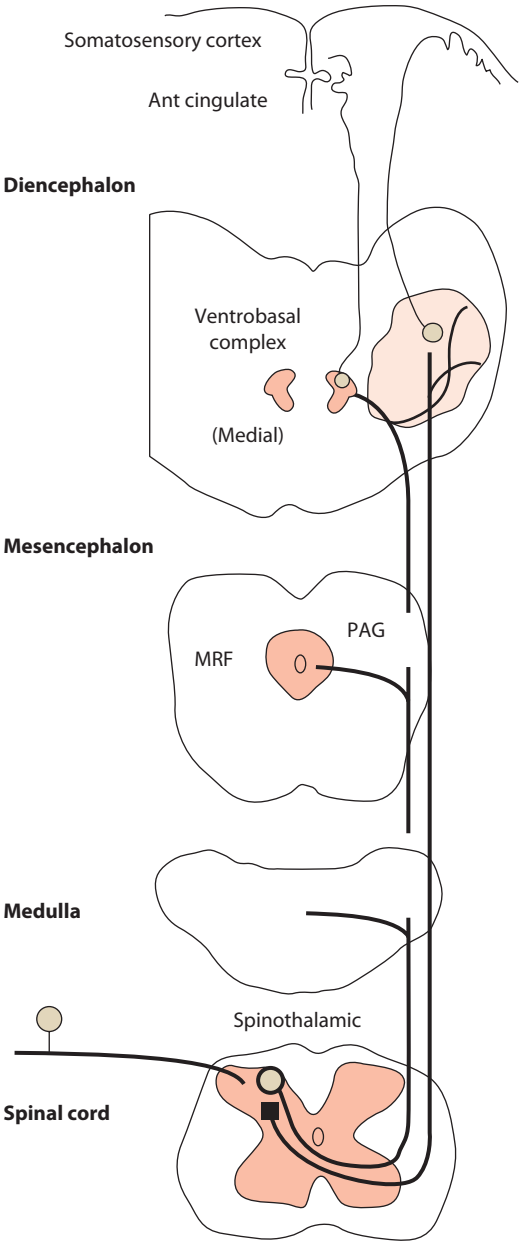

FIGURE 1-10. Sensory input into the spinal cord leads to the local activation of complex linkages that eventually project rostrally in the contralateral-ventrolateral pathways to medullary and diencephalic structures. In this schematic organization, it is emphasized that these ascending projections provide input in the lateral thalamus, which is somatotopically organized and projects from there into the somatosensory cortex. Importantly, a significant portion of the ascending traffic travels medially and makes synaptic contact in these medial regions with ascending projections that travel to the limbic cortex, such as the anterior cingulate cortex. Organizationally, it has been suggested that these different projection targets reflect upon substrates that underlie the "sensory-discriminative" and "affective-motivational" aspects of the pain experience.

In some instances, it is believed that the modulation may serve to diminish the pain message (i.e., endogenous analgesic systems). However, as subsequently discussed, there are several circumstances in which a repetitive afferent drive results in the involvement of an active facilitation of the message. In other cases, the nonaversive nature of large afferent stimulation (Aβ) reflects the continued presence of small inhibitory interneurons that alter large afferent input, but have no effect on activity in C fibers.

DYNAMIC ASPECTS OF ENCODING OF INJURY-GENERATED INPUT

The preceding section emphasized that tissue injury yielded activity in small primary afferents and that small afferent input resulted in monosynaptic and polysynaptic excitation of dorsal horn neurons that projected to the brainstem and higher centers. Importantly, the pathway appears to preserve several properties of the stimulus, the anatomic sign (localization), and intensity. Thus, input from an area of skin might be expected to activate a given population of spinal neurons that received afferent input from that part of the body surface, and the intensity of the stimulus was mirrored either by the specific neuronal population activated (e.g., nociceptive specific cells) or by the frequency of the discharge (as with the WDR neurons), or both. This linkage, even in its simplest form, would be described as the "pain pathway" as it reflects the connectivity by which afferent traffic generated by tissue injury reaches higher centers and the conscious state. This afferent substrate, in fact, represents only one component of the system that is essential to the processing of nociceptive input. The excitation of dorsal horn neurons evoked by small afferent input is subject to modulation by a number of receptor systems within the spinal cord. Technically, this modulation may be thought of in terms of those systems that increase or decrease the efficacy of synaptic connections of the afferent pathway.

PLASTICITY OF THE ENCODING OF PERSISTENT AFFERENT INPUT

Acute activation of small afferents by high-intensity mechanical or thermal stimuli will result in a clearly defined pain behavior in humans and animals. This event is believed to be mediated by the release of the excitatory afferent transmitters outlined earlier and, consequently, the depolarization of projection neurons. The magnitude of the response of a dorsal horn neuron, either WDR or nociceptive specific, is related to the frequency (and identity) of the afferent input.

The frequency of the afferent input is proportional to the magnitude of the acutely applied stimulus. The organization of this system's response to an acute stimulus is thus typically modeled in terms of a monotonic (linear) relationship between activity in the peripheral afferent and the activity of neurons that project out of the spinal cord to the brain.

As previously noted, in the face of tissue injury, the afferent input is characterized by a persistent afferent barrage. As discussed subsequently, such input reveals the initiation of a variety of inhibitor and facilitatory processes that lead to a nonlinear increase in spinal output.

INTRINSIC MODULATORY PROCESSES

The activation of dorsal horn neurons by afferent input can be modulated in such a fashion as to be decreased by several discrete systems.

Large Afferent Axon Interactions Dorsal horn WDR neurons can be inhibited by transient activation of large primary afferents. Such inhibition is mediated by a local spinal circuit that produces primary afferent depolarization (PAD), which exerts an inhibitory effect on the terminals of adjacent afferents. This serves to reduce the amount of neurotransmitter released from the afferent fibers in response to a fixed input. PAD is mediated by release from local interneurons in the substantia gelatinosa of the inhibitory amino acids, γ-aminobutyric acid (GABA) and glycine.[21] In human psychophysical studies, vibratory stimuli applied to a painful area served to activate large myelinated fibers and reduced perception of chronic musculoskeletal pain. Dorsal column stimulation by antidromically activating collaterals of large primary afferent fibers would also induce PAD, and this mechanism may account for some of the antinociceptive actions of dorsal column stimulation.

It is important to appreciate that the presence of these small inhibitory interneurons is crucial for the ongoing encoding of large afferent input. Thus, the spinal action of $GABA_A$ and glycine receptor inhibitors will induce a potent tactile allodynia. These results suggest that the nonaversive characteristics of large afferent stimulation depend upon this ongoing modulation. Studies in nerve injury–induced pain states have suggested that there is a loss of glycine or GABAergic inhibition secondary to the loss of dorsal horn neurons. The reduction in such inhibition may provide a partial explanation of the potent allodynia that accompanies such nerve injury states. An alternative event is that in the face of chronic inflammation and nerve injury, that there is a change in the expression of a neuronal chloride transporter that leads to an increase in intracellular Cl. In this case, opening a chloride ionophore will lead to an *exit* of anions that results in membrane *depolarization*. This anomolous event results in the GABA A and Glycine channels transitioning from an inhibitory to an excitatory phenotype.[22] Thus, the very circuit that would otherwise reduce large afferent excitation would itself become facilitatory.

Bulbospinal and Spinal Modulation Considerable evidence indicates that a variety of spinal terminal systems may serve to modulate nociceptive processing at the level of the spinal dorsal horn. Early work demonstrated that activation of bulbospinal pathways would suppress spinal nociceptive processing and produce a behaviorally defined analgesia by the release of noradrenaline and the activation of dorsal horn α_2 receptors. Evidence that small afferent activation could indirectly activate systems that mediated the spinal release of hormones, such as enkephalin or noradrenaline, which could act at such modulatory receptors, supported the perspective that nociceptive processing was under a tonic endogenous inhibition. In spite of the observation that activating these receptors (e.g., spinal injection of opiate and α_2 agonists) could yield a powerful analgesia by an action pre- and postsynaptic to the small afferent terminal, the delivery of antagonists for these receptors has surprisingly modest effects on spontaneous pain thresholds. This suggests that however potent a modulatory system these several receptors represent, these endogenous systems are not in a tonically active mode, and downregulation of small afferent input is not a pervasive component of the ongoing processing of input generated by tissue injury.

INTRINSIC FACILITATORY PROCESSES: REPETITIVE SMALL AFFERENT INPUT

WDR neurons in the spinal and medullary dorsal horn display a stable response to the discrete, periodic activation of afferent C fibers. However, repetitive stimulation of C (but not A) fibers at a moderately faster rate results in a progressively facilitated discharge. This facilitated response is called "wind-up" (see Fig. 1-9). This condition has three properties:

1. The conditioning serves to enhance the response of the dorsal horn neuron to subsequent input, such that a given stimulus yields a greater response that would otherwise be anticipated from that stimulus.
2. The conditioning of the spinal cord with repetitive small afferent stimulation has the additional effect of increasing the receptive field size of the neuron. Thus, afferent input from dermatomal areas that previously did not activate the WDR neuron being studied now evokes a prominent response. The anatomic substrate for this increased receptive field size is believed to reflect the otherwise weak excitatory input that comes from collaterals of afferents innervating the skin areas adjacent to the injury. In the face of the induction of a facilitated state in the specific neuron under study, this otherwise ineffective excitatory drive becomes adequate to drive depolarization. Intracellular recording reveals that the facilitated state reflects a progressive and sustained partial depolarization of the cell, rendering the membrane increasingly susceptible to afferent input.
3. Low-threshold tactile stimulation also becomes increasingly effective in driving these neurons. This facilitation by repetitive C-fiber input, therefore, increases the subsequent neuronal response to low-threshold afferent input and enhances the response generated by a given noxious afferent input. These mechanisms are discussed further in the next sections.