Handbook of Acute Pain Management

Edited by
Jennifer A. Elliott
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I would like to dedicate this book to my parents, David E. and Christel M. Elliott, and my husband, Michael J. Bell, who have provided much guidance, unconditional love and support, and the inspiration to complete this book.

I would also like to give thanks to the many contributors for their time and effort, as well as Dean Shepard for his assistance with creating many of the figures and tables in this book.

J.A.E.

Preface

Pain is a universal experience and is the most frequent reason people seek medical attention. Medical students and residents receive comprehensive guidance in the evaluation and diagnosis of the source of pain complaints, yet formal education on the topic of pain *symptom* management has not traditionally been offered in medical training, leaving many clinicians uncomfortable with providing treatment for pain. Pain can therefore become ''painful'' to the treating practitioner as well as the patient. This book is intended to assist clinicians who are called upon to treat the patient in acute pain by enhancing their knowledge of and comfort with pain therapies. The scope of providers who may be in a position to manage the acute pain patient is wide ranging, from medical students and residents to primary care providers, as well as anesthesiologists, neurologists, physiatrists, and other specialists.

This book will provide the reader with background information on the anatomy and neurobiology of pain to lay a foundation for the understanding of pain pathophysiology. Pharmacologic approaches to acute pain management are thoroughly covered, including the use of local anesthetics, NSAIDS, opioids, and α_2 agonists. Patient-controlled analgesia options including patient-controlled epidural analgesia are also explored. Nonpharmacologic and interventional anesthetic techniques are covered, including the use of continuous catheter techniques for postoperative pain management. A chapter also reviews information about anticoagulation guidelines when considering the use of regional and neuraxial anesthetic techniques. Finally, a discussion of pain management issues in special populations such as pediatric, obstetric, trauma, opioid-tolerant, and elderly patients is provided.

The material in this book is intended to provide an up-to-date look at the emerging treatment strategies in the continuously expanding field of pain management and is accompanied by numerous figures and tables to give an at-a-glance review of important concepts discussed in the text. This text provides expanded information on topics such as opioids, including potential drug-drug and drug-disease interactions, which cannot readily be found in other similar texts currently on the market. It also highlights the evolution of new technologies such as ''smart'' patient-controlled analgesia devices along with associated safety innovations. Information on new developments in the field of regional anesthesia, especially the emergence of continuous catheter techniques, is included to bring the reader up to date on the latest available injection-based therapies.

My goal is that readers will find this book to be a user-friendly reference that addresses the most recent developments in the management of pain. I hope this will assist readers in the approach to the patient suffering acute pain and will enhance their level of comfort as well as that of their patients.

Jennifer A. Elliott

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1 The anatomy of postoperative pain

Jun-Ming Zhang

INTRODUCTION

Postoperative pain or postsurgical pain can be considered a form of acute nociceptive pain with localized inflammatory responses resulting from surgical tissue damage (1). Pain is termed "nociceptive" when the clinical evaluation suggests that it is sustained primarily by the nociceptive system. Nociceptive pain is pain that is proportionate to the degree of actual tissue damage. This "good" pain serves a positive and protective function. Postoperative pain can be neuropathic or neurogenic and can become chronic if it involves inflammation or injury to a nerve, which can occur during surgical procedures such as amputation, hernia repair, hand surgery, or thoracotomy. It is estimated that about 80% of patients experience pain after surgery, of which 86% have moderate, severe, or extreme pain (2–4). In spite of considerable progress in postoperative analgesia, recent studies show that adequate pain relief remains elusive for a significant fraction of hospitalized surgical patients (5–7). It is important for health care professionals to have an understanding of the anatomy and physiology of postoperative pain to improve outcomes in managing postoperative pain.

ANATOMY OF POSTOPERATIVE PAIN

Understanding the physiology and pathophysiology of postoperative pain requires basic knowledge of the anatomy, such as pathways mediating the perception of somatosensory stimuli under normal physiological conditions.

The first step in the pain process involves the transduction of the sensory stimulus (e.g., mechanical, thermal, or chemical) into electrical pulses by primary afferent neurons whose cell bodies reside in the dorsal root ganglion (DRG). These neurons express specialized receptors at their distal ends, which respond to specific types of external (e.g., the skin) or internal (e.g., visceral organs) sensory stimuli by generating electrical pulses or action potentials, which propagate to the dorsal horn of the spinal cord. In general, DRG neurons can be classified as large, medium, and small, which are associated with Aβ-, Aδ-, and C-fibers, respectively. Large-diameter DRG neurons possess large myelinated axons with rapid conduction velocities greater than 15 m/sec and generally transmit information about innocuous mechanosensation (touch, vibration, or pressure). Noxious stimulation is transmitted via small-diameter DRG neurons, which give rise to either thin myelinated A-fibers (which conduct impulses at 2–15 m/sec) or small unmyelinated C-fibers (with conduction velocities of <2 m/sec). Table 1.1 summarizes the properties and functions of three main primary afferent fibers in pain sensation under physiological and pathophysiological states.

The signals carried by primary sensory afferents are integrated by the synaptic network within the spinal dorsal horn, which consists of both local circuit interneurons and second-order projection neurons, which transmit electrical impulses from the spinal cord to higher brain areas predominantly via the

TABLE 1.1 Properties and Functions of Primary Afferent Fibers

Fiber type	Anatomy	Threshold	Main transmitters	Main receptors activated	Laminar level	Target spinal neurons	Normal function	Pathological function
C	Small unmyelinated	High	Peptides (SP, CGRP)	NK 1, 2	I–II, V	NS	Slow pain	Hyperalgesia
Aδ	Small myelinated	Low and high	EAA (glutamate)	NMDA AMPA mGlu	I–II, V	WDR	Fast pain	Allodynia
Aβ	Large myelinated	Low	EAA (glutamate)	AMPA	III–VI	LT WDR	Touch vibration Pressure	Mechanical allodynia

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CGRP, calcitonin-gene related peptide; EAA, excitatory amino acids; LT, low threshold; NK, neurokinin receptor; NMDA, *N*-methyl-D-aspartate; NS, nociceptive specific; SP, substance P; WDR, wide dynamic range.

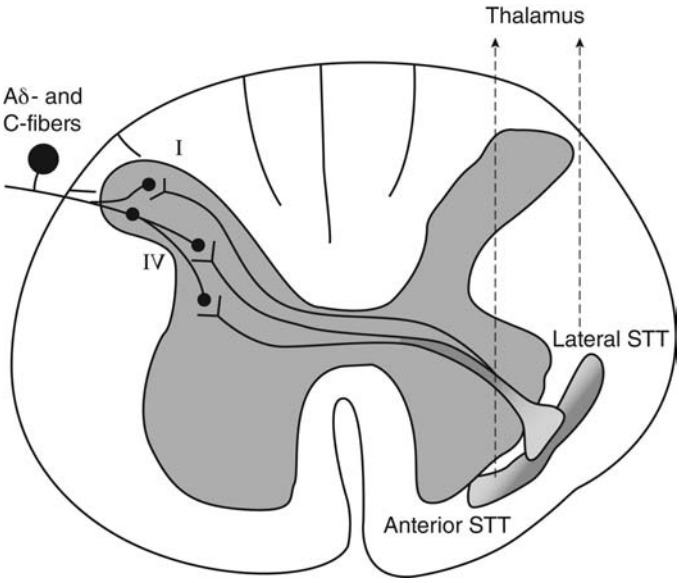

FIGURE 1.1 Pain pathway. *Abbreviation*: STT, spinothalamic tract.

spinothalamic tract (STT) (Fig. 1.1). The output of these STT neurons depends on the net balance between inhibitory and facilitatory mechanisms within the dorsal horn. For example, repetitive stimulation of tactile Aβ mechanoreceptive inputs can activate spinal interneurons and inhibit the response of STT neurons by decreasing the amount of glutamate released from the presynaptic terminals of nociceptive C-fibers. This is believed to underlie the effectiveness of both transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) as clinically therapeutic interventions for patients with pain. In contrast, responses of STT neurons to nociceptive stimuli can be facilitated if they have been subjected to long-term excessive input from C-fiber nociceptive neurons, which can be caused by chronic inflammation or other chronic noxious stimulation of C-fibers. The excitability of STT neurons is also modulated by descending projections to the spinal cord from higher areas of the CNS, such as the rostral medulla, which can cause both facilitation and inhibition under different conditions.

The activation of third-order neurons in the thalamus by STT inputs allows the transmission of the noxious information to the cerebral cortex, where the perception of pain is generated. Evidence exists that many supraspinal control areas, such as the reticular formation, midbrain, thalamus, hypothalamus, the limbic system of the amygdala and the cingulate cortex, basal ganglia, and cerebral cortex, modulate the sensation of pain.

MECHANISMS OF POSTOPERATIVE PAIN

Like pain resulting from acute tissue injury, postoperative pain involves sensory, emotional, and cognitive components. This chapter focuses on the sensory changes contributing to the postoperative pain: peripheral and central sensitization. Since damage or inflammatory irritation of peripheral nerve endings near the surgical

site is considered the main cause of postoperative pain, we also discuss the neuropathic mechanisms in the pathogenesis of peripheral and central sensitization, and chronic postoperative pain.

Peripheral and Central Sensitization in Postoperative Pain

Surgical tissue damage results in the elevation of an enzyme, cyclooxygenase-2 (COX-2), in inflammatory cells (e.g., neutrophils and mast cells) and leads to the production and release of inflammatory mediators such as histamine, bradykinin, serotonin, and prostaglandins. In response to local chemical release, unmyelinated C-fibers and small myelinated Aδ-fibers will be sensitized and generate electrical pulses at the nerve endings. This is referred to as "peripheral sensitization," in contrast to central sensitization, which occurs at the dorsal horn. Substance P may also be released peripherally with resultant increase in peripheral vasodilatation and further sensitization of the peripheral endings of C/Aδ-fibers. Other chemical mediators, such as ATP and protons, can directly activate the ends of the peripheral nociceptors, signaling the presence of inflamed tissue and producing pain. Inflammatory cytokines released from damaged tissues, such as tumor necrosis factor α (TNF-α), may contribute to peripheral sensitization by direct activation of nociceptive fibers (8,9).

Following peripheral nerve lesion, strong sustained activation of nociceptive afferents, particularly C-fiber nociceptors, may lead to sensitization of dorsal horn neurons (i.e., "central sensitization"). This can result in the following alterations in the physiological properties of dorsal horn neurons: (*i*) increased size of the receptive field (i.e., the area of the body, which, when stimulated, evokes action potential firing in the cell); (*ii*) lower thresholds; neurons begin to fire in response to low-threshold afferent inputs that were previously too weak to evoke action potential discharge; (*iii*) increased magnitude of action potential discharge in response to nociceptive inputs; and (*iv*) increased spontaneous impulse activity. These alterations are thought to significantly contribute to the hyperalgesia, allodynia, and spontaneous pain that result from peripheral nerve injury.

Most research data on postoperative pain were obtained from basic research in animal models and human subjects (10). In a rat incisional pain model developed by Brennan et al., it was found that surgical incision in the plantar aspect of the rat hindpaw caused mechanical hyperalgesia to punctate and nonpunctate stimuli that closely parallels that seen in the patients during their postoperative course (11). Enhanced withdrawal response to punctate stimuli was observed in injured and uninjured tissues, suggesting that both primary and secondary hyperalgesia had developed. Further study discovered that *N*-methyl-D-aspartate (NMDA) receptor-mediated secondary hyperalgesia is short lasting in this model. Thus, on the basis of animal research, primary hyperalgesia is the most important mechanism in incisional pain. However, other research studies indicate that central sensitization may be important in the pathogenesis of viscerovisceral and viscerosomatic pain (12). Thus, it is likely that the underlying mechanisms of postoperative pain are associated with the types of surgical procedures performed.

Surgical Neuropathic Pain

Overall, surgery accounts for 10% to 30% of clinical neuropathic pain (13). Certain surgical procedures such as mastectomy, axillary clearance, thoracotomy, amputation, and herniorrhaphy have had higher prevalence rates varying between

TABLE 1.2 Comparison of Nociceptive and Neuropathic Pain

Nociceptive pain	Neuropathic pain
Pain caused by tissue injury	Pain caused by nerve injury
Stimulus evoked, high intensity	Spontaneous, evoked activity
Develops instantly	Develops in days or months
C-fiber mediated	A-fibers involved, low threshold
Opioid sensitive	Poorly opioid responsive

30% and 70% (14,15). Neuropathic pain is characterized by the factors listed in Table 1.2, and while it can be caused by injury to any component of the peripheral nervous system, it is most often associated with the peripheral nerve. It is a condition that develops after the original injury and is manifested by both spontaneous pain and evoked activity that is interpreted out of proportion to the intensity of the stimulus. In addition to C polymodal nociceptive fibers, it is apparently also mediated by low-threshold mechanosensitive A-fibers, since pain can be induced by light touch of the mechanoreceptors. Unlike nociceptive pain, neuropathic pain may respond poorly to traditional pain medications, including opioids. The well-established peripheral and central mechanisms of neuropathic pain can be briefly summarized as follows.

Ectopic Discharges and Ion Channel Alteration in Axotomized Sensory Neurons

Spontaneous activity is rarely observed in normal axons or DRG cells. However, this is a common phenomenon after the peripheral axons are injured. There is now compelling evidence that the expression of sodium channel subtypes (e.g., Nav1.3, Nav1.7, Nav1.8, and Nav1.9) is dramatically altered by nerve injury and may account for the increased excitability of DRG neurons after peripheral nerve injury. Recent works show that elevated chemokines, such as GRO/KC, in the DRG play a pivotal role in nerve injury-induced alteration of sodium channel expression (16).

A reduction in the density of potassium channels following axotomy may also increase the excitability of sensory neurons. This is supported by observations that mexiletine, which can lead to an attenuation of neuropathic pain, also facilitates K^+ currents in DRG neurons.

Previous work has also demonstrated that peripheral nerve injury causes alterations in voltage-sensitive Ca^{2+} channels in DRG neurons. Since these channels are involved in controlling the release of neurotransmitters from the terminals of sensory, central, and sympathetic neurons in the spinal cord, these alterations have significant implications on nociceptive processing under pathological conditions. In fact, the ability of anticonvulsants (e.g., carbamazepine and gabapentin) to reduce mechanical allodynia may involve, among other mechanisms, an interaction with Ca^{2+} channels localized on the injured DRG neurons.

Anatomical Changes in the Axotomized DRG: Sympathetic Excitation of Injured Sensory Neurons

Complex regional pain syndrome (CRPS) is a neuropathic pain condition that can occur after surgery. The key symptom of CRPS is continuous, intense pain out of proportion to the severity of the injury, which gets worse rather than better over time. Typical features include dramatic changes in the color and temperature of the

skin over the affected limb or body part, accompanied by intense burning pain, skin sensitivity, sweating, and swelling. Although the mechanisms are not clear, in some cases the sympathetic nervous system plays an important role in sustaining the pain. Clinical observations and animal studies have shown that coupling of the activated sympathetic nervous system and the sensitized sensory nervous system is important for the development of sympathetically mediated pain (SMP). Under normal physiological conditions, the afferent sensory nervous system and the efferent sympathetic nervous system are anatomically separated and functionally independent of each other. There is evidence, however, that abnormally enhanced communication between these two systems may occur under pathological conditions. For example, sympathetic stimulation may excite sensory neurons in animals with inflamed peripheral tissue or following peripheral nerve injury. Extensive sympathetic sprouting occurs in the sensory ganglia after peripheral nerve injury. It has been reported that sprouted fibers may enwrap large and medium neurons and form basket-like structures (17,18). These observations suggest that increased activity of the sympathetic nervous system may be involved in the sensitization of sensory neurons toward the development of neuropathic pain. Clinically, it is found that chemical or surgical sympathectomy or sympathetic ganglionic blockade relieves allodynia and hyperalgesia and improves chronic pain in some human patients.

Long-Term Potentiation of Nociceptive Inputs in the Dorsal Horn

The repetitive activation of high-threshold C-fibers, as might occur at the time of surgery damaging a peripheral nerve, can result in a prolonged increase in the strength of their synaptic connections with dorsal horn neurons. The result is that a given impulse from the nociceptive fiber can produce a greater depolarization of second-order neurons in the spinal cord. Importantly, in lamina I of the dorsal horn, this potentiation of synaptic efficacy occurs selectively on spinal projection neurons (i.e., the output cells of the dorsal horn). Thus, strong activation of nociceptive sensory afferents can lead to a greater synaptic drive onto spinal projection neurons and a subsequent facilitation of pain transmission from the spinal cord to the brain.

The activation of the NMDA subtype of glutamate receptor is necessary to induce long-term potentiation in the superficial dorsal horn. Within lamina I of the spinal cord, activation of the substance P receptor NK1 is also required. Animal studies have confirmed that both NMDA and NK1 receptors are involved in the induction and maintenance of central sensitization produced by high-threshold nociceptive afferent inputs at the behavioral level. Because central sensitization is likely to contribute to postinjury pain hypersensitivity states in man, these data have a bearing on the potential importance of NMDA and NK1 antagonists for preemptive analgesia and the treatment of established pain states. However, it should be noted that other types of receptors such as metabotropic glutamate receptors and TrkB receptors are also capable of inducing synaptic plasticity in the dorsal horn.

Spinal Glial Activation

There is now significant evidence showing that glial activation in the spinal cord appears to be important for both the initiation and maintenance of pathological pain (19). Spinal glia (e.g., astrocytes and microglia) are activated after peripheral nerve injury (20,21). Activation of spinal glia leads to the release of mediators that

then act on other glia and spinal neurons. The released chemicals, including proinflammatory cytokines (e.g., interleukin-1 and TNF-α), have been shown to be critical mediators of allodynia (19).

EFFECTIVENESS OF NERVE BLOCKADE AND STEROID ON POSTOPERATIVE PAIN INDUCED BY NERVE INJURY

There has been ample evidence supporting the efficacy of preemptive analgesia on postoperative pain. However, most studies have focused on skin infiltration of local anesthetics such as bupivacaine for acute postoperative pain (22–24). Data about whether ectopic discharges generated at the injury site contribute to the development of persistent pain is scarce. Recently, our laboratory has been assessing long-term effects of early nerve blockade and corticosteroid on nerve injury–induced neuropathic pain (25).

Using rat models of neuropathic pain, we show that local, temporary nerve blockade of afferent activity originating at the injured nerve permanently inhibits the subsequent development of both thermal hyperalgesia and mechanical allodynia. Timing is critical—the nerve blockade must last at least 3 to 5 days, and is effective if started immediately after nerve injury but not if started at 10 days after injury when neuropathic pain is already established (24). Nerve blockade proximal to the injury site of the sciatic nerve also reduced abnormal sympathetic sprouting in the axotomized DRG, a well-known phenomenon implicated in neuropathic pain (18). These results indicate that early spontaneous afferent fiber activity is the key trigger for the development of pain behaviors and suggest that spontaneous activity may be required for many of the later changes in the sensory neurons, spinal cord, and brain observed in neuropathic pain models. Many preclinical and clinical studies of preemptive analgesia have used much shorter duration of blockade or have not started immediately after the injury. Our results suggest that effective preemptive analgesia can be achieved only when nerve block is administered early after injury and lasts several days. Our studies suggest that local anesthetics with long-lasting effects should have a better impact on postoperative pain and possibly prevent the transition of acute pain to a persistent state.

In another study, we examined the effects of systemic administration of the corticosteroid triamcinolone acetonide (TA; Kenalog®) on mechanical pain behaviors and abnormal sympathetic sprouting in a rat model of neuropathic pain (26). TA was injected subcutaneously once per day for four days beginning on the day of surgery. It was found that early treatment with TA significantly decreased mechanical allodynia and sympathetic sprouting, with both effects lasting after cessation of steroid treatment. However, TA was without effect when given after mechanical pain behaviors were established. The observation that TA was effective when given starting at the time of injury, indicating the same effect as early nerve blockade, suggests that anti-inflammatory steroid treatment might alter the development of postoperative pain after certain surgical procedures that involve nerve injury.

CONCLUSION

Understanding the anatomy of acute and neuropathic postoperative pain requires knowledge of the underlying neuronal plasticity at the levels of the nociceptive neurons, spinal cord, and brain. Modulatory effects at the nociceptor, SMP, central sensitization, and alterations in ascending/descending CNS pathways are all involved in the perception of pain as well as the related pain motivations and

behaviors. Recent findings from laboratory experiments have provided encouraging information toward the clinical management of postoperative pain.

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2 The neurobiology of acute pain

Eugene E. Fibuch and John Q. Wang

INTRODUCTION

The onset of an acute pain event is distinctly characterized by a complex neurobiology involving multiple processes that go beyond the traditional understanding of neuroanatomic pathways (1–3). The most common definition of acute pain is the normal predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma or acute illness (4). Yet, it is well recognized that patients' experiences, attitudes, beliefs, and personalities have a strong influence on how they respond to and perceive an acute pain event. Merskey and Bogduk noted that acute pain usually lasts less than a month, but could be evident up to six months following tissue injury (5). Despite the time differentiation noted in the literature between acute and chronic pain states, there is a growing body of evidence suggesting that the seeds of a chronic pain state are implanted very early on following the onset of acute pain (6,7). Therefore, acute pain should be considered as a potential cause of a persistent chronic pain state, if not corrected in a timely manner (4).

This chapter will not detail the neuroanatomy of the classic afferent pain pathways since this has been previously well documented in the literature. Instead, this chapter will concentrate on more recent developments emphasizing the pharmacological, immunohistochemical, and genetic factors that contribute to our understanding of how acute tissue injury (incision, inflammation, contusion, ischemia, or disease) causes afferent nociceptive signaling to the conscious brain. In addition, the mechanisms of chronic pain will not be addressed in detail, except in those areas where the impact of an acute pain signal could alter the neural environment that might initiate the development of a chronic pain state. A better understanding of these physiological, pharmacological, and genetic factors may help provide the basis for a more informed approach to the management of acute pain.

PAIN PHYSIOLOGY

The modern understanding of the mechanisms of acute pain has evolved from the classic work of Descartes in the 17th century, who thought that acute pain transmission occurred through anatomically distinct neural pathways from skin receptors to the spinal cord tracts. These spinal cord tracts, primarily the spinothalamic tract, would then conduct signals to the brain, where conscious perception of the noxious event is perceived. Presently, our understanding recognizes that the perception of acute noxious signaling involves a very dynamic process in both the peripheral and central nervous systems (CNS) in which the afferent signal can be augmented, diminished, or redirected to either the ventral horn of the spinal cord or to the sympathetic ganglia where autonomic and/or motor responses (reflexes) can be initiated. Clinical studies suggest that the intensity of the acute pain signal may be an important predictor of the development of a chronic pain state (8). In addition, intense nociceptive input from the periphery to the CNS can result in

central sensitization in which the nociceptive signaling may persist long after the primary insult to tissue has disappeared. This can result in hypersensitivity and hyperexcitability of the pain conducting pathways, both centrally and peripherally (1). The spinal circuitry appears to have the ability, under these conditions, to undergo considerable change. This has been referred to as dorsal horn plasticity, which is pivotal to the development of the hypersensitivity state (9). Also, acute pain can transition to a chronic pain state in which acute nociceptive stimuli can produce aberrant gene expression in the dorsal horn of the spinal cord (10). This gene expression has been noted in specialized dorsal horn neurons, primarily the wide–dynamic range (WDR) neurons. Although a number of genes appear to be involved in this process, the most studied genetic locus is the c-fos oncogene, which is thought to be a protein encoder for the neuropathic pain state (11).

The process of creating a painful stimulus is the result of a complex series of biochemical and electrical events summating in the conscious experience of pain. This process is the composite of four distinct subprocesses, which have been identified as: transduction, transmission, modulation, and perception (3). Beaulieu and Rice have previously described these four subprocesses in the following way: "Transduction or receptor activation, is the process by which external noxious energy is converted into electrophysiological activity in nociceptive primary afferent neurons. Transmission refers to the process by which this coded information is relayed to those structures of the CNS concerned with pain. The first stage of transmission is the conduction of impulses in primary afferent neurons to the dorsal horn of the spinal cord, from which a network of neurons ascends in the spinal cord to the brainstem and thalamus. Finally, reciprocal connections are made between the thalamus and the multiple higher areas of the brain concerned with the perceptive and affective responses associated with pain. However, nociceptive activity does not always result in pain perception (equally, pain may be perceived in the absence of tissue injury). Therefore, a process of signal modulation must be introduced into this system that is capable of interfering in this 'pathway.' The modulatory site about which most is known is the dorsal horn of the spinal cord. The final process is perception, in which the pain message is relayed to the brain, producing an unpleasant sensory experience, which has affective, defensive, and perceptive components (3)."

Acute nociceptive signals begin with tissue injury. Action potentials are created in afferent neurons that respond to a variety of noxious stimuli, such as mechanical, chemical or thermal action potentials. Nociceptive firing of afferent neurons increases following noxious stimulation. Although there is some specificity in terms of the response of the peripheral nociceptors, the majority of the nociceptors respond in a polymodal manner to a variety of painful inputs (12). In addition, the response of these polymodal nociceptors is in proportion to the logarithm of the stimulus applied. Once tissue injury occurs, a variety of tissue factors are released, which can cause tissue edema, vasodilatation, and the induction of an inflammatory state (13,14). These factors include potassium and prostaglandin (PG) from the injured tissue, cytokines and histamine from mast cells, tissue accumulation of serotonin (liberated from platelets), and bradykinin (plasma kininogen) from the vasculature. In addition, adenosine triphosphate (ATP) and nitric oxide (NO) are released. Endogenously produced PG, bradykinin, and a variety of cytokines are potent stimulants of the peripheral pain receptors (12). These compounds are released primarily as a result of the initiation of the arachidonic acid pathway (13). Of importance, the inflammatory mediators act to

modify the response of primary afferent neurons to subsequent stimuli resulting in a state of increased peripheral nerve sensitivity (13). Finally, C-fibers release substance P and calcitonin gene-related peptide (CGRP), which can sensitize both the local afferent neurons and their associated peripheral nociceptors. These mediators can sensitize nociceptors (lower the neuronal threshold) or activate dormant (silent) nociceptors, in addition to increasing the rate of neural discharge and the rate of spontaneous discharge (4,15).

Once the peripheral nociceptors have been activated, afferent transmission of the nociceptive signal occurs via three primary somatosensory afferent neural pathways, which have been classified as Aβ-, Aδ-, and C-fibers (16). Each of these fiber types responds differently, and they synapse in the spinal cord at different locations (16).

The thickly myelinated Aβ-fibers transmit nonnoxious, low-intensity mechanical signals from specialized encapsulated receptors on their peripheral nerve endings at a rate of approximately 7 to 75 m/sec. These fibers terminate in the deeper layers of the dorsal horn, primarily in laminas III, IV, and V before their signals are projected to the brain, primarily via the spinothalamic tract. Of note, Aβ-fibers synapse on WDR neurons, which are located in lamina V, potentially modulating the output of the WDR neurons.

The Aδ-fibers, which are less heavily myelinated, conduct both nonnoxious and noxious (thermal and/or mechanical) signals at a slower conduction velocity of 2 to 7 m/sec. In addition, the Aδ-fibers receive afferent nociceptive signals from high-threshold mechanoreceptors. They distribute these signals to not only the deeper portions of the spinal cord (similar to the Aβ-fibers in lamina V), but they also synapse in the more superficial layers of the dorsal horn (similar to the C-fibers in lamina I).

The C-fiber is the smallest and slowest conducting of the three fiber types, transmitting at a rate of 0.5 to 1.5 m/sec. C-fibers are specialized in that they conduct polymodal (i.e., respond to a full range of mechanical, thermal, and chemical stimuli) noxious signals from free peripheral nerve endings and are the most numerous of the somatic nociceptors (3,16). Furthermore, from a histochemical perspective, the C-fibers are further divided into IB4-positive (plant derived isolectin) and tyrosine kinase receptor (TrkA)-positive [nerve growth factor (NGF)] types (16). C-fibers terminate on second order neurons located primarily in the superficial layers of the spinal cord, lamina I (marginal zone) and lamina II (substantia gelatinosa). From these superficial connections, second order neurons transmit C-fiber input to the deeper layers of the cord, primarily to the WDR neurons in lamina V.

The WDR neurons receive afferent input from many different first order neurons in the dorsal horn. This is referred to as convergence, which allows the WDR neuron to fire more action potentials in response to noxious stimuli. The majority of nociceptive signaling, however, occurs via Aδ- and C-fibers. At the same time, not all Aδ- and C-fiber transmission encodes for a painful stimulus. Some signaling from these peripheral neurons may encode for innocuous temperature, itch, and touch sensations (12). In addition to the primary afferents, signaling may occur via specialized afferent fibers, which have been referred to as "silent" neurons. They were first identified in joint tissue and later found in visceral and cutaneous tissue (11). They are activated only when there has been significant tissue injury (12).

Nociception of viscerally mediated pain is not as well understood. Thermal and mechanical stimuli, which are potent stimulants of somatically mediated pain,

do not appear to initiate pain from visceral organs. However, pathological distension or contraction of visceral structures, such as obstruction of the intestines, induces a painful reaction. The question that has been raised is whether there are specialized visceral nociceptors that respond to pressure changes in the walls of visceral organs. There is some evidence to suggest that there may be either pressure sensitive receptors in the muscular walls of visceral organs or specialized neurons that respond to high-intensity stimuli (3). In addition, visceral afferent signaling may have monosynaptic input to the central canal of the spinal cord (lamina X) (12). New models for studying visceral pain have been recently introduced, which may help delineate this issue in the future (17).

Following first order synaptic transmission in the spinal cord, the afferent signal is processed by three different neuronal cells. These neuronal cells consist of projection neurons, inhibitory, or excitatory interneurons. They conduct the afferent signals via spinal tracts that ascend anterolaterally in the contralateral spinal cord to the thalamus (3). Signals coming from the body are transmitted through the brainstem to the thalamus, while those coming from the head enter the thalamus via the midbrain. Signals may also connect to the ventral horn neurons, facilitating motor reflex responses and/or sympathetic responses via the spinal sympathetic ganglion. The dorsal horn of the spinal cord thus acts as a master integrator of nociceptive signals (18). Pain transmission can be directed to the autonomic centers of the brain, which regulate the cardiovascular and respiratory functions of the body, or to the limbic system, where affect and emotion are imprinted into the pain signaling process. Nociceptive information is then processed into consciousness (2,12).

Pain transmission may occur via ipsilateral projecting neural systems such as uncrossed components of the spinothalamic, spinoreticular, and spinomesencephalic tracts (19). The dorsal horn neurons act to direct, reduce, and amplify nociceptive signaling utilizing multiple mechanisms. These include neural inhibitory neurons (descending posterior column), sometimes referred to as diffuse noxious inhibitory controls, and the WDR neurons located in lamina V (4).

In addition, acute nociceptive transmission to the CNS results in a neuroendocrine stress response, which includes the release of not only local inflammatory mediators (cytokines, PG, leukotrienes) but also systemic mediators of the stress response such as cortisol, adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), glucagon, aldosterone, renin, catecholamines, and angiotensin II (20). The stress response may trigger additional unwanted events, such as hypercoagulability, inhibition of fibrinolysis, increased platelet activity, and may potentiate postoperative immunosuppression (21,22).

NEURONAL PLASTICITY AND PAIN

A greater understanding of the biochemical changes that occur in the dorsal horn following nociceptive signaling has been achieved in recent years (13,23,24). A diverse group of membrane-bound ionotropic and metabotropic glutamate receptors are located throughout the CNS. The former is divided into three major subclasses: AMPA, kainite, and NMDA receptors (25). With nontissue damage-related nociceptive signaling, the excitatory amino acid receptor AMPA (α-amino-3-hydroxy-5-methy-soxazole acid) is stimulated in the neural cell membrane of the dorsal horn. However, with more repetitive stimulation, such as resulting from tissue damage, a second excitatory amino acid receptor also located on the neural

cell wall, the NMDA receptor (*N*-methyl-D-aspartate), is stimulated (13). The major excitatory neurotransmitter that activates these receptors is glutamate. Glutamate produces a fast response depolarization in the dorsal horn neurons primarily via the NMDA receptor. In addition, it can activate the metabotropic glutamate receptors (mGluRs) which are linked to intracellular G proteins (23). Activation of the NMDA receptor leads to increased excitability of dorsal horn neurons and increased calcium flux (12). Intracellularly, activation of Gαq protein–coupled group 1 mGluRs induces calcium release from stores found in the endoplasmic reticulum, as well as activation of protein kinase C (PKC). PKC phosphorylates the NMDA receptor, releasing the magnesium (Mg^{2+}) plug within the NMDA channel, allowing cell membrane depolarization to occur (13). Calcium is also involved in a number of other intracellular cascades such as the activation of a variety of enzymes and protein kinases (12). This intracellular process is significantly more complicated than described, and therefore, the reader is referred to a more in depth discussion of this intracellular cascade (23). In addition, NMDA receptors have been identified on unmyelinated and myelinated axons in peripheral somatic tissue, suggesting that they have not only a central role in nociceptive signaling, but also a peripheral role (26). They also appear to play an important, if not a pivotal role, in the development of spinally mediated hyperexcitability and the development of chronic pain (27). The development of a hyperexcitable state may result from changes that occur in the NMDA receptor mRNA expression pattern following peripheral stimulation (25). A more detailed description of the role of mRNA expression can be found in the work of Petrenko and coworkers (27).

RECEPTORS AND NEUROTRANSMITTERS INVOLVED IN PAIN SIGNALING

In addition to the more widely known AMPA, kainate, and NMDA receptors, a series of ion channel–linked receptors related to sensory transduction of noxious stimuli have recently been described (13,24,28). Three types of receptors have been defined and include the vanilloid receptor (VR)-1, the acid-sensing receptor, and the purinergic receptor. The VR-1 is primarily distributed in small diameter afferent neurons throughout the CNS. It is sensitive to capsaicin and to moderate thermal stimuli. The acid-sensing receptor is part of a group of ion channels that are selectively activated by protons, are found throughout the CNS, and appear to be activated by inflamed tissue, arthritic joints, and ischemia (29). The purinergic receptors are phosphate derivatives of AMP, ADP, and ATP (13). They mediate fast synaptic transmission via extracellular ATP, which is released by the somatic cell following tissue injury, or in the presence of tumors, inflammation, migraine headaches and visceral distension. Purines appear to cause pain by initiating the release of other inflammatory mediators. ATP acts extracellularly at two P2 purinergic receptors, either the P2X (ligand-activated cationic channel) receptor or the P2Y (G protein–coupled) receptor (30).

Various voltage-gated ion channels, which are membrane proteins forming temporary permeable pores between the extra- and intracellular spaces, have been noted to play an important role in nociceptive transmission (13). The two most important ion channels appear to be the sodium and calcium channels. The sodium channels have been classified into two types on the basis of their sensitivity to tetrodotoxin (TTX): TTX-resistant (TTX-R) and TTX-sensitive (TTX-S) channels. Large diameter afferent fibers express only TTX-S sodium channels, while the small

diameter afferent fibers express both TTX-R and TTX-S sodium channels (13). During different types of nerve injury, the response of the sodium channels may differ. For example, during acute nerve injury it appears that there is a decrease in the expression of TTX-R channels and an increase in TTX-S channels. However, following an inflammatory pain event there is an increase in the expression of TTX-R channels and a reduction in the expression of TTX-S channels (31). The variable response of the TTX-R and the TTX-S channels to different nociceptive stimuli may explain why there is variability in patient responses to the use of local anesthetics and anticonvulsants for the treatment of pain. These agents work by blocking sodium channels and thus offer a potentially attractive opportunity to control pain transmission at the cellular level. Calcium channels also play a role in transmission of afferent signaling; however, the therapeutic benefit of blocking their function in acute pain states has not been fully elucidated. The N-type calcium channel, which is found specifically on neuronal membranes, appears to have potential for therapeutic channel blockade (32). This is the mechanism by which the conotoxin, ziconotide, is presumed to relieve pain.

Substance P has been known for some time to be an important transmitter of nociceptive signaling (10). It is synthesized in the small diameter afferent fibers and is transported to the CNS, where it is stored in vesicles in the cell bodies of the afferent fibers. Substance P is a member of a family of tachykinins, which include neurokinin (NK)-A and NK-B. These peptides target specific tachykinin receptors: NK-1, NK-2, and NK-3 receptors, which are found in the dorsal horn neurons (1). During an acute noxious stimulus, it appears that substance P acts only in the region of lamina I and II rather than throughout the entire dorsal horn, however it can stimulate the WDR neuron via dorsal horn interneurons (1). This peptide causes the degranulation of mast cells with resultant release of histamine. Vasodilatation and plasma extravasation can result, causing the release of bradykinin and serotonin, both of which are powerful inflammatory and nociceptive mediators (11). In addition, substance P can induce the production of NO, which is another powerful vasodilator released from the endothelium of the vasculature. Intracellularly, substance P activates phospholipase C (PLC), which increases inositol 1,4,5-triphosphate (IP) and diacylglycerol (DAG), resulting in an increase in intracellular calcium. The rise in intracellular calcium alters phosphorylation and gene expression of proteins and induces cellular depolarization, which in turn are implicated in the regulation of nociceptive transmission (23).

Another nociceptive substance released during tissue/nerve damage is nerve growth factor (NGF), which is not only important in the development of sensory and autonomic nerves, but appears to play a role in the process of nociception (33). It is released in the periphery by Schwann cells and fibroblasts and can in turn increase excitability of the peripheral nociceptors on primary sensory nerve terminals to promote thermal hypersensitivity. NGF selectively interacts with its receptor, TrkA, and has the ability to sensitize both cutaneous and visceral primary afferent nociceptors and recruit the silent nociceptors (23). Also, NGF not only has an impact on the primary nociceptive afferent, but can stimulate mast cells and sympathetic efferent nerves. NGF regulates the responsiveness of nociceptors to bradykinin and the sensitivity of the sodium channels located on sympathetic neurons (23).

The PGs are weak in their ability to stimulate nociceptive neurons; however, they appear to be important in the process of sensitizing nociceptive receptors to other compounds (11). Following tissue injury, arachidonic acid is formed from phospholipase, which results in the transformation to three other compounds:

thromboxane, prostacyclins, and PGs. The PGs, particularly from the E and F series, act on specific PG receptors to increase the amount of neurotransmitter released, thus magnifying the transmitted response (12,34). All PG receptors are G protein coupled and when activated trigger intracellular changes in calcium, cAMP, and phosphoinositol concentrations (34). In addition, these receptors show large differences in affinity for and reactivity under various ligands. When PGs are given to test animals intrathecally, the animals demonstrate two types of responses. The first is an increase in response to noxious stimuli (hyperalgesia) and the second is the response of allodynia (touch-evoked pain). This response occurs within minutes of the administration of PG and the dose response curve appears to be bell shaped (34). For a more in depth review of the role of PGs in nociceptive transmission, the reader is referred to an article by Vanegas and Schaible (34).

INHIBITORY COMPONENTS IN PAIN TRANSMISSION

Up to this point, the discussion of the nociceptive system has been related to the afferent excitatory component. There is, however, a powerful inhibitory component to the nociceptive signaling system. The raphe nuclei, periaqueductal gray and the nucleus gigantocellularis exert inhibitory actions on spinal processing of afferent nociceptive signaling (23). These brainstem nuclei form the basis of the descending inhibitory system, which travels caudally to the spinal cord via the posterior descending columns and links to the afferent neurons and interneurons in the dorsal horn. This linkage is referred to as presynaptic inhibition and is thought to reduce the probability of action potentials or inhibit neurotransmitter release by restricting the calcium influx into nerve terminals (23). Second order neurons in the dorsal horn also can receive synaptic connection with the descending fibers, which is referred to as postsynaptic inhibition. This inhibitory system depends on inhibitory neurotransmitters such as γ-aminobutyric acid (GABA), catecholamines, glycine and serotonin, as well as the endogenous opioid system. GABA and glycine are thought to exert inhibitory control over the Aβ primary afferents and the second order neurons in the dorsal horn (35). The GABA receptor exists in two forms, GABA-A and GABA-B. Both have different functions in the spinal cord, as they respond to different agonists. For example, GABA-A will respond to the benzodiazepines while GABA-B will respond to baclofen, a non-benzodiazepine compound. There is some evidence that following nerve injury there is a loss of GABAergic function, which may explain the loss of inhibitory control noted in neuropathic pain states (36).

Finally, recent findings suggest that inflammatory induced nociceptive signaling to the dorsal horn evokes synaptic rearrangement, which may actually strengthen the nociceptive neural connections that result in a chronic pain state (23). In addition, posttranslational and transcriptional changes appear to occur in second order neurons in the spinal cord. These changes lead to an increase in excitability. By inducing the activity of primarily the NMDA receptor, IP is activated intracellularly, which increases the activity of calcium and calcium-sensitive signaling pathways.

The transcriptional system is then initiated, allowing the inducible expression of proto-oncogenes to occur (23). The end result is the protein encoding of a hypersensitivity state and the potential for the development of a long lasting chronic pain state (24).

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3 Local anesthetics in the management of acute postoperative pain

Gary McCleane

INTRODUCTION

Conventional treatment of postoperative pain revolves around the use of opioids, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics. Utilization of such drugs has been accepted for many years, and yet we still have not optimized our use of them. When specifically considering local anesthetics, novel formulations, and new uses of currently available preparations give the prospect of increasing the quality of postoperative pain relief. It is therefore possible that with imaginative use of these drugs, even though they have been available for many years, increased levels of postoperative pain relief may be produced while the need for other systemically active compounds may be reduced. When considering postoperative pain, and indeed any acute pain, a nociceptive stimulus (e.g., surgical incision, tissue reaction to trauma) precipitates a nociceptive stimulus from periphery to spinal cord and hence to the brain. This structure responds by adding an affective component and by initiating descending inhibitory and facilitatory drives. With the local anesthetics we have an opportunity to intervene at the periphery, along the peripheral nerves, and even at the cord level in an attempt to block this nociceptive process.

When we consider local anesthetics, we have certain drugs in mind. Lidocaine and bupivacaine are good examples. By implication, we are talking about drugs with sodium channel blocking effects and, from a clinical perspective, drugs that have numbing or freezing effects when applied locally. A number of other drugs also possess these local anesthetic effects by virtue of their sodium channel effects, and are yet not conventionally classified as local anesthetics. For example, tricyclic antidepressants and a number of the antiepileptic drugs have known sodium channel effects. In this chapter, we will confine our attention to those drugs conventionally referred to as local anesthetics.

MODE OF ACTION OF LOCAL ANESTHETICS

The intimate relationship between the activity of the membrane bound enzyme, Na^+-K^+ ATPase, and propagation of nerve impulses is firmly established. The ionic disequilibrium across the semipermeable membrane in a nerve produces the potential energy for an action potential with the disequilibrium being rectified by the activity of Na^+-K^+ ATPase. Local anesthetics block impulses by inhibiting individual Na^+ channels, and thereby reducing the aggregate inward sodium current (1–3). When used at sufficient concentration, local anesthetics can cause complete neural blockade with obvious consequences on motor and sensory function of the nerve involved. However, when agents such as lidocaine are administered systemically at lower doses, no effect is apparent on the conduction of action potentials in normal Aβ, Aδ, or C primary afferents (4). In contrast, systemic lidocaine significantly suppresses the C-fiber evoked polysynaptic reflex generated by nerve stimulation. At concentrations of 1 to 20 μg/mL, lidocaine

reversibly suppresses the tonic action potential discharge of acutely injured nerves and axotomized dorsal root ganglion cells (5–7).

Even when given in doses sufficient to cause significant cardiovascular side effects, lidocaine reduces the conduction in uninjured Aδ-fibers by less than 5%, and in C-fibers by under 50%, demonstrating that when lidocaine is administered systemically at reasonable dose levels, "normal" neural function is essentially uninterrupted, while a measurable effect is observed in damaged neural tissue (8,9).

It has also recently been shown that when lidocaine is administered systemically in animal models, sympathetic noradrenergic sprouting from damaged dorsal root ganglia is significantly reduced when compared with control animals. Of particular note is that this effect persists for more than seven days after the cessation of lidocaine administration. This persistence of effect from systemic lidocaine is again seen when frog sciatic nerves are treated with this drug, causing a rapid, concentration-dependent decrease in the action potential plateau with this effect lasting for over one hour after washout of lidocaine (10).

CLASSIFICATION OF LOCAL ANESTHETICS

Ester-Linked Local Anesthetics

- Cocaine
- Procaine (Novocain®)

Procaine Analogs

- Tetracaine (Pontacaine®, Amethocaine®)
- Benzocaine (Hurricaine®, Solarcaine®, Dermoplast®)
- 2-Chloroprocaine (Nesacaine®)

Amide-Linked Local Anesthetics

Aminoacyl Amides

Aminoalkyl xylidide family.

- Lidocaine (Xylocaine®)
- Prilocaine (Cintanest®)
- Etidocaine

Pipecolyl xylidide family.

- Mepivacaine (Polocaine®, Carbocaine®)
- Bupivacaine (Marcaine®, Sensorcaine®)
- Ropivacaine (Naropin®)

Aminoalkyl Family

- Procainamide
- Dibucaine

CLINICAL USES OF LOCAL ANESTHETICS

Topical

Gels/Creams

Several topical local anesthetic preparations are available in gel, cream, and patch form. Tetracaine is available as a gel, and lidocaine/prilocaine are presented in a eutectic mixture as EMLA® cream. EMLA cream use has become established in the

anesthetizing of skin prior to cannula insertion. It also has demonstrable benefit in reducing the pain of other procedures including lumbar puncture, intramuscular injections, and circumcision (11). Caution should be used with long-term use of this preparation, as prilocaine use has been associated with the onset of methhaemoglobinaemia.

Patches

Lidocaine is available in a topically applied patch in a 5% strength (Lidoderm®). In the United States, lidocaine 5% is approved by the FDA for the treatment of postherpetic neuralgia (PHN). Its efficacy in this pain condition is supported by several trials, which also confirm that it is well tolerated (12–15). Not only can pain levels in patients with PHN be reduced, but measures of quality of life show improvement. In one study of patients with PHN, 66% of subjects reported reduced pain intensity when up to three lidocaine 5% patches were used for 12 hours each day (16).

While lidocaine 5% has an indication for use in PHN, it may also be efficacious in other pain conditions. When used in the treatment of focal neuropathic pain conditions, such as mononeuropathies, and intercostal or ilioinguinal neuralgia, one controlled study has confirmed a pain reducing effect (17,18). In an open-label study of 16 patients with "refractory" neuropathic pain (including patients with postthoracotomy pain, complex regional pain syndrome, postamputation pain, neuroma pain, painful diabetic neuropathy, meralgia paresthetica, and postmastectomy pain), 81% of subjects experienced pain relief. In this report, refractory was used to describe those patients who had either failed to gain pain relief, or those who experienced unacceptable side effects with opiates, anticonvulsants, antidepressants or antiarrhythmics agents.

It is intriguing to speculate what pain relieving effect topical application of lidocaine 5% patch might have on postoperative pain. If it were prepared in a sterile form, then it could be applied directly over a wound site and changed on a daily basis. Where pain would be expected to be largely local and of body wall in origin, such as in the case of inguinal hernia repair or after mastectomy, then it is reasonably likely that it may reduce pain. Suitable studies are needed to verify or refute this speculation.

Infiltration

Infiltration of local anesthetic around a surgical wound is now accepted practice. A variety of local anesthetics can be used, always remembering the potential for them to cause systemic toxicity if used in excessive doses. In the case of lidocaine, which can cause vasodilatation, the maximum safely administered dose can be increased and its duration of effect lengthened by the addition of epinephrine. In the case of other local anesthetics such as levobupivacaine, bupivacaine, and ropivacaine, the addition of epinephrine has little to no influence on the maximum dose to be administered or on duration of effect. When epinephrine is considered, it should not be injected into any area adjacent to an end artery, or peripheral ischemia may result.

While local infiltration offers significant analgesic benefit, the commonly utilized local anesthetics have finite durations of action, and so at some stage, pain is expected to return. Currently, investigation is ongoing into extended duration of effect of local anesthetics with which duration of effect may be measured in days rather than hours.